INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

SOME PLANTS AS A SOURCE OF ACETYL CHOLINESTERASE INHIBITORS: A REVIEW

Purabi Deka *, Arun Kumar, Bipin Kumar Nayak, N. Eloziia
Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology & Science, Dehradun, India
*Corresponding Author Email: purabi3010@gmail.com

Article Received on: 27/03/17 Approved for publication: 27/04/17

DOI: 10.7897/2230-8407.08565

ABSTRACT

The term dementia derives from the Latin *demens* ("*de*" means private, "*mens*" means mind, intelligence and judgment- "without a mind"). Dementia is a progressive, chronic neurological disorder which destroys brain cells and causes difficulties with memory, behaviour, thinking, calculation, comprehension, language and it is brutal enough to affect work, lifelong hobbies, and social life. Alzheimer's disease, Parkinson's disease, Dementia with Lewys Bodies are some common types of dementias. Acetylcholinesterase AChE) Inhibition, the key enzyme which plays a main role in the breakdown of acetylcholine and it is considered as a Positive strategy for the treatment of neurological disorders. Currently many AChE inhibitors namely tacrine, donepezil, rivastigmine, galantamine have been used as first line drug for the treatment of Alzheimer's disease. They are having several side effects such as gastrointestinal disorder, hepatotoxicity etc, so there is great interest in finding new and better AChE inhibitors from Natural products. Natural products are the remarkable source of Synthetic as well as traditional products. Abundance of plants in nature gives a potential source of AChE inhibitors. The purpose of this article to present a complete literature survey of plants that have been tested for AChE inhibitory activity. Many phytoconstituents and promising plant species as AChE inhibitors are being reported in this communication.

Keywords: Plants, Acetylcholine, Acetyl cholinesterase inhibitors, Alzheimer's disease, Dementia

INTRODUCTION

A process for acquiring memory is called as learning and a behavioural change caused by an experience is termed as memory. Without memory, we are not capable of doing anything because it is the major fundamental process[1]. Memory is divided into three classes depending on the amount of time the memory lasts: sensory memory, short-term memory, and long-term memory. Sensory memory that is also called as shortest-lived memory and it lasts only milliseconds to a few seconds[2]. Short term memory or immediate memory explained the brain's ability to store information on a timescale of seconds or less and which lasts from several seconds to at most a few minutes[2,3]. The long-term memory lasts anywhere from an hour to lifetime and it is normally believed to lack details[2,4]. But it is well confirmed that long-term memory can store a huge number of items[4]. Neurodegenerative disease describes the various conditions which is raised from chronic breakdown and deterioration of the neurons, specially neuron of central nervous system. In case of elderly people dementia is a most common neurodegenerative disease. Dementia is a syndrome generally associated with the progressive and chronic retardation of intellectual functioning[5]. More precisely, dementia defined as significant cognitive impairment which is not a specific disease but a group of symptoms that can be caused by a number of disorders that affect the brain[6]. It destroys the vital brain cells, causing difficulty with memory, thinking, behaviour, orientation, language and judgment, brutal enough to affect work, lifelong hobbies and social life[7,8]. Women between the age group of 75 - 79 years and men of same age group account to 5.7% and 15.7% of dementia sufferers respectively[9]. WHO projections suggested that about three-quarters of the population aged 60 or over will be living in developing countries by 2025[10]. The number of people affected by dementia will double between 2020 (42 million) and 2040 (81 million)[11]. There are several types of dementia, among them Alzheimer's disease (AD) is the most common cause of dementia (60%), followed by vascular dementia (VaD) (20% of people have both AD and VaD) and dementia with Lewy bodies (DLB) (15%)[12]. Today's many synthetic drugs originated from the plant kingdom, and our pharmacopoeia was dominated by herbal medicines only about 200 years ago[13]. Medicinal plants play an important role in the health care of ancient As well as modern cultures. The Indian system of medicine, Ayurveda, mainly uses plant based drugs or formulations to treat many human diseases due to their therapeutic value[14]. Historically, many different plant sources have been used to treat learning and memory associated deficits. Moreover, a growing interest has risen about the value and use of natural resources for their efficacy in the treatment and improvement of cognitive impairments, Alzheimer's disease (AD) along with its associated pathologies[15].

CHOLINESTERASES

Cholinesterase which is a family of enzymes that activates the hydrolysis of the neurotransmitter acetylcholine (ACh) into choline and acetic acid. This reaction is required to allow a cholinergic neuron to return to it's resting state after activation[16]. It involves two types of enzymes:

Acetylcholinesterase (AChE)

It is found in high concentration in all types of Conducting tissues, nerve and muscle, central and peripheral tissues, motor and sensory fibres, sympathetic and parasympathetic fibres which are also called cholinergic and non -cholinergic fibres. The concentration of the enzyme is high in all the regions where cell bodies and junctions are located[17]. AChE which is a serine hydrolase well known for it's role in terminating synaptic

transmission and preventing continuous nerve firings at nerve endings which is essential for the normal functioning of the central and peripheral nervous system[18,19]. The AChE molecule is constituted of two different protein domains. One is a large catalytic domain of about 500 residues and another one is a small C-terminal peptide of less than 50 residues. The active site of AChE involves two subsites: the anionic site and the esteratic subsite. The positive quaternary amine of acetylcholine binds to the anionic subsite and acetylcholine is hydrolyzed to acetate and choline in the esteratic subsite. The carboxyl ester hydrolysis into to an acyl-enzyme and free choline. Then, by a water molecule the acyl-enzyme undergoes nucleophilic attack, release acetic acid and regenerate the free enzymes[18]. AChE EC 3.1.1.7 composed of a complex protein of the α/β hydrolase fold type which is having an overall ellipsoid shape containing a deep groove. Generally, it is called the gorge which is about 20A˚ deep. The esteratic site has the catalytic machinery of the enzyme. This is dependent on a catalytic triad of Ser200–His440–Glu327 which is used by Cholinesterases to enhance the nucleophilicity of the catalytic serine. The "oxyanion hole" (OH) consists of Gly118, Gly119 and Ala201[20]. The oxyanion hole which is containing these three peptide residues is a more valuable motif for the stabilization of the tetrahedral intermediate of Ach than the corresponding two-pronged structures in serine proteinases[20, 21]. The "anionic subsite" which is also known as choline-binding subsite or hydrophobic Subsite, is largely comprised of aromatic residues and it has Trp84, Phe330 and Glu199. The "peripheral anionic site" (PAS) varies among AChEs. It is composed of aromatic and carboxylic acid residues, Asp72, Tyr70, Tyr121, Trp279, and Phe290 in *Tc*AChE. The "acyl pocket" which is also called as acyl binding pocket or acyl-binding pocket, composed of Phe288 and Phe290. These are believed to play a role in regulating the dimension of substrates which are able to enter the active site[20]. Generally, AChE is present in three isoforms and they are G1 in brain, G4 in brain and neuromuscular end plate and G2 in skeletal muscle and blood forming cells[5].

Butyrylcholinesterase(BuChE)

It is also known as pseudocholinesterase or nonspecific cholinesterase which is a serine hydrolase that catalyses the hydrolysis of esters of choline[22]. BChE is widely distributed in liver, intestine, heart, kidney and lung[23].

ACETYLCHOLINESTERASE INHIBITORS

Anti-Cholinesterase inhibitors (e.g. drugs, natural toxins, pesticides, chemical warfare agents) are a large group of chemical compounds with different physico-chemical properties which inhibit the cholinesterase enzyme from breaking down ACh, increasing both the level and duration of the neurotransmitter action[16, 24]. AChE inhibitors can be divided into two groups: irreversible and reversible**.** Reversible inhibitors mostly have therapeutic applications[16]. Compounds which inhibit AChE can be divided into three basic groups: Compounds those bind at the active site interact with either esteratic such as nerve agents or anionic site such as tacrine, Compounds those interact with the aromatic gorge such as decamethonium and Compounds those bound at the peripheral (β) anionic site such as huperzine, propidium *d*-tubocurarine[24].

HERBAL DRUGS AS CHOLINESTERASE INHIBITORS

For the discovery of new drugs, natural products remain a prolific source and these new drug leads even from Vedic period. Recent data proposed that 80% drug molecules are natural products (NPs) or natural compound inspired[25]. Herbal medicines are still the backbone of about 75 – 80% of the world population, mostly in the developing countries for primary health care because of their better compatibility and cultural acceptability with the human body and lesser side effects[26]. A variety of plants has been reported to show AChE inhibitory activity and so may be suitable to the treatment of various neurodegenerative disorders such as AD. Ethno pharmacological approaches as well as bioassay guided isolation have given a lead to find possible AChE and BuChE inhibitors from plants including those for memory disorders[5].

ALKALOIDS AS ACHE INHIBITORS

In case of alkaloids inhibitors, binding take place at the active site at the bottom of the gorge and important features of the inhibitor seem to be positively charged nitrogen. It binds to the oxyanion hole area, mainly Trp84 and a region which is separated by a lipophilic area from the positive charge. It can form hydrogen bonds with the serine 200 residue and other such as His 440 of the catalytic traid inhibiting AChE activity. Some inhibitors bind to the both peripheral anionic site and at the bottom of the gorge[5].

Table 1: Alkaloids as AChE inhibitors from plants

S.N	Active constituent	Family	Plant name	Plant part and extract used	Class of compound	Ref no
1.	Lycorine, Tazettine, Crinine,3-epi-hydroxybulbispermine,2-demethoxy-montanine, Galanthamine	Amaryllidacae	*Galanthus ikariae*	Bulb and Chloroform: methanol	Alkaloid	27
2.	Conypododiol	Asparagaceae	*Asparagus adscendens*	Aerial parts and Ethanolic	Alkaloid	28
3.	Bulbocapnin, corydaline	Fumariaceae	*Corydalis cava*	Tubers and Methanolic	Alkaloid	29
4.	N-methylasimilobine	Nelumbonacae	*Nelumbo Nucifera*	Leaves and Ethanolic	Alkaloid	30,31
5.	Annotinine, Annotine, Annotine N-oxide, Lycodoline, Lycoposerramine M Anhydrolycodolin, Gnidioidine Lycofoline, Acrifoline	Lycopodiaceae	*Lycopodium annotinum*	Aerial parts	Lycopodane-type alkaloid	32,27
6.	Buxakarachiamine, Buxakashmiramin,	Buxaceae	*Buxus papillosa*	Leaves and Ethanolic	Triterpenoid alkaloid	33,27

	Buxahejramine, Cyclomicrophylline-A, Cyclovirobuxeine-A, Cycloprotobuxine-C					
7.	Stepharanine, cyclanoline and *N*-methyl stepholidine	Menispermaceae	*Stephania venosa*	Ethanolic extract	Quaternary protoberberine alkaloids	34
8.	Juliflorine	Papilionaceae	*Prosopis juliflora*	Leaves	Piperidine alkaloids	5
9.	Dehydroevodiamine	Rutaceae	*Evodia rutaecarpa*	Whole plant, Methanolic	Quinazoline alkaloid	35,27
10.	(–)-huperzine A	Lycopodiaceae	*Huperzia serrata*		Quinolizidine alkaloid	36,27
11.	Trigonelline	Leguminosae	*Trigonella foenum graecum L*	Seed, Ethanol	Alkaloid	37,38
12.	Isotalatizidine hydrate	Ranunculaceae	*Delphinium denudatum*	Aerial parts, Methanolic	Diterpenoid alkaloids	39

INDOLE ALKALOID AS AChE INHIBITORS

In the carbamate moiety of the drug, the carbonyl group interacts with the hydroxyl group of serine200 which is present in the catalytic traid of AchE to form an ester in the urethane parts of the molecule. This interferes with the AChE inhibitory property of the enzyme and the ester is slowly hydrolyzed to regenerate the active parent form. Therefore, carbamate group acts as a key reason in the AChE inhibitory activity. Moreover, the presence of aromatic ring and a nitrogen atom facilitates the binding of inhibitors to AChE, interfering with its activity[5].

Table 2: Indole alkaloids as AChE inhibiotrs from plants

S.N.	Active constituent	Family	Plant name	Plant parts used	Class of compound	Ref no
1.	Physostigmine	Leguminosae	*Physostigma venenosum*	Seeds	Indole alkaloid	40, 37
2.	Rutaecarpine and dehydroevodiamine	Rutaceae	*Evodia rutaecarpa (Juss.) Benth.*		Indole alkaloid	37
3.	Geissospermine	Apocynaceae	*Geissospermum vellosii Allemao*	Stem bark	Indole alkaloid	37
4.	Serpentine	Apocynaceae	*Catharanthus Roseus*	Root	Indole alkaloid	41
5.	LegusinA	Papilionaceae	*Desmodium pulchellum* and *D. gangeticum*		Indole alkaloid	5
6.	Turbinatine and desoxycordifolie	Rubiaceae	*Chimarrhis turbinata*	Leaves and bark	Indole alkaloid	5
7.	Uleine	Apocynacea	*Himatanthus lancifolius*,		Indole alkaloid	34

ISOQUINOLINE ALKALOID AS ACHE INHIBITORS

In alkaloids with bezylisoquinoline structure the AChE inhibitory property because of the presence of quaternary nitrogen atom at the tetrahydroisoquinoline part of alkaloids[5].

Table 3: Isoquinoline alkaloids as AChE inhibitors from medicinal plants

S.N.	Active constituent	Family	Plant name	Plant parts and extract used	Class of compound	Ref no
1.	Protopine	Papaveraceae	*Corydalis ternate*	Tuber and methanolic	Isoquinoline alkaloid	42
2.	berberine	Huang Lian	*Rhizoma Coptidis*		Isoquinoline alkaloid	43,44
3.	Corynoline	Papaveraceae	*Corydalis incise*	Aerial parts and Methanolic	Isoquinoline alkaloid	5
4.	Palmatine, corynoxidine	Papaveraceae	*Corydalis speciosa*	Aerial parts and methanolic	Isoquinoline alkaloid	45

STEROIDAL ALKALOIDS AS AChE INHIBITORS

Galanthamine which is a steroidal alkaloid and it is isolated from *Galanthus nivalis* (common name Snowdrop) and *Galanthus woronowii* (family Amaryllidaceae), *Narcissus* spp. (common name Daffodil), *Leucojum* spp. (common name Snowflake), and Lycoris including *Lycoris radiata* (common name Red spider Lily)[46]. Galanthamine binds at the base of the active site gorge of AChE which interacts with both coline –binding site as well as acyl binding pocket[5]. A structure activity relationship study showed that the hydroxyl group at C-3 on galantamine gives to it's effective binding to AChE. On the cholinergic system Galantamine has a dual action mechanism. It inhibits AChE and allosterically modulates nAChR activity. Galantamine binds to brain AChE and it reduces ACh catabolism which increases ACh levels in the synaptic cleft[46].

Table 4: Steroidal alkaloids as AChE inhibitors from medicinal plants

S.N.	Active constituent	Family	Plant name	Plant parts and extract	Class of compound	Ref no
1.	Assoanine	Amaryllidaceae	*Narcissus assoanus*	Dormant Bulb and methanolic	Steroidal alkaloid	47, 27
2.	11-hydroxygalantamine	Amaryllidaceae	*Narcissus poeticus*	Dormant Bulb and methanolic	Steroidal alkaloid	47, 27
3.	Sanguinine	Amaryllidaceae	*Eucharis grandiflora*	Dormant Bulb and methanolic	Steroidal alkaloid	47, 27
4.	Epinorgalantamine	Amaryllidaceae	*Narcissus confuses, Narcissus perezchiscanoi, Narcissus leonensis, Narcissuslegionensis, Narcissus poeticus*	Dormant Bulb and methanolic	Steroidal alkaloid	47, 27
5.	Homomoenjodaramine, moenjodaramine	Buxaceae	*Buxus hyrcana*		Steroidal alkaloid	3
6.	Hookeriana H, Hookeriana I, Sarcovagine C, Epipachysamine D, Dictyophlebine	Buxaceae	*Sarcococca hookeriana*		Pregame type steroidal alkaloid	3
7.	Sarsalignone, Vaganine,	Buxaceae	*Sarcococca saligna*		Steroidal alkaloid	48, 27
8.	Buxamine B	Buxaceae	*Buxus hyrcana, Buxus papillosa*		Steroidal alkaloid	48, 27
9.	Isosarcodine , Sarcorine , Sarcodine , Sarcocine , Alkaloid-C	Buxaceae	*Sarcococca saligna*	Whole plant and methanolic	Steroidal alkaloid	49, 27

TERPENOIDS AS AChE INHIBITORS

Terpenoids are consists of large group of natural products and it is composed of two or more branched 5 carbon units which is formed from a common precursor called mevalonic acid. Terpenoids can be divided in many groups such as monoterpines which is having 10 carbons in the structure, sesquiterpines which is containing 25 carbons, diterpines and triterpines which is containing 20 and 30 carbons in the structure[5].

Table 5: Terpenoids as AChE inhibitors from plants

S.N.	Active constituent	Family	Plant name	Plant parts and extract	Class of compound	Ref no
1.	α-pinene, β-pinene	Lamiaceae	*Salvia potentillifolia*	Aerial parts and ethanolic	Monoterpene	50
2.	1,8-cineol, α-pinen	Lamiaceae	*Salvia lavandulaefolia*		Monoterpene	51
3.	Ursolic acid	Lamiaceae	*Origanum majorana*	Ethanolic	Pentacyclic triterpene acid	52
4.	(+)-limonene, trans-anethole, (+)-sabinene	Apiaceae	*Pimpinella anisoides*		Terpene	27
5.	β-asarone	Araceae	*Acorus Calamus*	Rhizome and Methanolic	Phenylpropanoids	53, 37
6.	Cryptotanshin,	Lamiaceae	*Salvia miltiorhiza Bunge*	Root, Acetone	Diterpenoids	37
7.	Taraxerol	Ericaceae	*Vaccinium oldhami*	Twigs	Triterpine	5
8.	(E)-β-caryophyllene, bicyclogermacrene	Compositae	*Gynura bicolor DC.*	Leaves and stem, diethyl ether	Sesquiterpines	54
9.	Marsupellin A ,Marsupellin B		*Marsupella alpine*	Whole plant, ethanolic	Sesquiterpenoids	55

FLAVONOID DERIVATIVES AS AChE INHIBITORS

According to Ji and Zhang (2006), flavonoid derivatives showed AChE inhibitory activity because of the presence of the catechol moiety in its structure[56].

Table 6: Flavonoid derivatives as AChE inhibitors from plants

S.N	Active constituent	Family	Plant name	Plant parts and extract	Class of compound	Ref no
1.	Isomucronulatol	Lamiaceae	*Micromeria cilicica*	Aerial parts	Isoflavone	57
2.	Sudachitin	Lamiaceae	*Micromerian cilicica*	Aerial parts	Polymethoxylated flavones	57
3.	Tiliroside, 3-Methoxy quercetin, Quercetin, Quercitrin	Rosaceae	*Agrimonia pilosa*	Whole plant, Methanolic	Flavonoid	58
4.	Sophoflavescenol, icaritin, demethyl anhydroicaritin, 8-C-lavandurylkaempferol and kaempferol	Fabaceae	*Sophora flavescens*		Flavonol	34
5.	quercetin-3-*O*-*β*-D-glucopyranoside, quercetin-3-*O*-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside	Ginkgoaceae	*Ginkgo biloba*	Leaves, Methanolic	Flavonol-*O*-glycosides	59
6.	Naringenin	Rutaceae	*Citrus junos*		Flavanone	20

GLYCOSIDE AS AChE INHIBITORS

Table 7: Glycoside as AChE inhibitors from plants

S.N	Active constituent	Family	Plant name	Plant parts and extract	Class of compound	Ref no
1.	Piperitone 7-O-b-D-glucoside	Lamiaceae	*Micromeria cilicica*	Aerial parts	Glycoside	57
2.	1,2,3,4,6-penta-O-galloyl-β-D-glucose	Combretaceae	*Terminalia chebula*		Glycoside	60, 27
3.	Cynatroside B, Cynatroside A	Asclepiadaceae	*Cynanchum atratum*		Pregnane glycoside	27
4.	Verbascoside	Scrophulariaceae	*Verbascum mucronatum Lam.*	Flower, Methanolic	Phenylethanoid glycoside	61
5.	Kaempferol 3-O-(600-O-E-p-coumaroyl)-b-glucopyranoside	Blechnaceae	*Stenochlaena palustris*	Fronds, Methanolic	Kaempferol glycoside	62

XANTHONE AS AChE INHIBITORS

Urbain *et al* reported that methanolic leaves extract of *Gentiana campestris* (family Gentianaceae) showed AChE inhibitory activity due to the presence of xanthones namely Bellidin, Bellidifolin, Bellidin 8-O-βBellidin 8-O-β glycopyranoside (Norswertianolin) and Bellidifolin 8-O-β glycopyranoside (swertianolin)[63]. In Bellidifolin absence of glucopyranosyl moiety increases the AChE inhibitory activity than other xanthones which is might be because of the steric factors or hydrophobicity. At it's C-3 position, presence of methoxy group increases inbitory activity[20].

LIGNANS AS AChE INHIBITORS

Tran Manh Hung *et al* reported that the hexane extract of the fruit of *Schizandra chinensis* (family Schisandraceae) was found to show remarkable acetylcholinesterase enzyme (AChE) inhibition activity due to the presence of lignans. In this study fourteen lignans were isolated, and evaluated for their AChE inhibitory effect. The compounds have both aromatic methylenedioxy and hydroxyl groups on their cyclooctadiene ring, such as gomisin C, gomisin G, gomisin D, schisandrol B and gomisin A, entirely inhibited AChE in dose dependent manners, with IC50 values of 6.71 ± 0.53, 6.55 ± 0.31, 7.84 ± 0.62, 12.57 ± 1.07 and 13.28 ± 1.68 μM, respectively. These results show that the lignans could be a potent class of AChE inhibitors. Gomisin D lesser active than gomisinC and G because of the presence of α-hydroxyl group at C-7, side chains at C-6 and C-14 and methylenedioxy groups at C-12 and C-13. Gomisin C and Gomisin G were having aromatic methylenedioxy, α-hydroxyl (C-7) as well as β-benzoyl (C-6) groups. Interestingly, Schisandrol B which contained a β-hydroxyl group at C-8 and methylenedioxy groups at C-2 and C-3 and Gomisin A which contained a β-hydroxyl group at C-7 and methylenedioxy groups at C-12 and C-13 showed much lower inhibitory activities than Gomisin C, Gomisin G and Gomisin D. This demonstrated that the presence of a hydroxy group, the β orientation might show a lesser inhibitory effect than the orientation. These results denoted that aromatic methylenedioxy and cyclooctadiene hydroxyl groups are having great significance for the AChE[5, 64].

Honokiol and Magnolol (lignans) were isolated from methanolic bark extract of *Magnolia officinalis* (family Magnoliaceae)[65] and these biphenolic lignans (honokiol and magnolol) inhibited AChE activity *in vitro*, increased ChAT activity and hippocampal ACh release *in vivo*[65,66]. 4-*O*-methylhonokiol which is isolated from the ethanol extract of the bark of *Magnolia officinalis* is also dose-dependently reduced the scopolamine-induced increase of acetylcholinesterase (AChE) activity in the cortex and hippocampus of mice as well as showed inhibition of AChE activity *in vitro* with IC_{50}(12 nM)[67].

POLYPHENOLS AS AChE INHIBITORS

Table 8: Polyphenols as AChE inhibitors from plants

S.N	Active constituent	Family	Plant name	Plant parts and extract	Class of compound	Ref no
1.	VitisinA , Heyneanol A	Vitaceae	*Vitis amurensis*	Root, butanolic	Polyphenol	5
2.	(+)-α-vinifer, kobophenol A	Leguminosae	*Caragana chamlague*	Methanolic, underground parts	Stilbene oligomer	27,68

Vitisin A is having a proper bulky structure masks AChE and suppresses Ach from binding to AChE in a non competitive manner. Heyneanol A which is also having a bulky structure and thebulky structure completely masks AChE as well as lowers the accessibility of substrate to AChE[5].

SHIKIMATE-DERIVED COMPOUNDS AS ACHE INHIBITORS

According to the Structural analysis most of the shikimate derived compounds which shows AChE inhibitory property, they show AChE inhibition activity because of the presence of one phenylpropanoid unit alone or two or more units combined[5].

Table 9: Shikimate –derivatives as AChE inhibitors from plants

S.N.	Active constituent	Family	Plant name	Plant parts, extract used	Class of compound	Ref no
1.	Esculetin and Daphnetin, Umbelliferone 6-carboxylic acid, Umbelliferone, Scopoletin, Isoscopoletin, 20 - isopropyl psoralene, 7-methoxy coumarin	Umbelliferae	*Angelica decursiva* and *Artemisia capillaris*		Coumarin	69
2.	Scopolatin	Ericaceae	*Vacinnium oldhami*	Twigs, Methanolic	Coumarin	70
3.	Xanthotoxin, Isopimipne	Apiaceae	*Angelica aqutiloba*	Root	Furanocoumarins	5
4.	Murranganin Hainanmurpanin	Rutaceae	*Murraya paniculata*		Pyrenlated coumarin	5

Esculetin and Daphnetin, showed the highest AChE inhibitory activity due to the the presence of an O-dihy droxyl (Catechol) group. Umbelliferone own a free hydroxyl group at the 7 position while umbelliferone 6-carboxylic acid is having both a free hydroxyl group at the 7 position and a carboxylic group at position 6. Interestingly, though there is difference in structure, the latter compound possesses inhibitory activity which is lesser than Esculetin and Daphnetin. Substitution with a methoxyl or glycosyl group reduced the inhibitory potential as shown by the activity of scopoletin, isoscopoletin, scopolin, scoparone, and 7-methoxy coumarin. 20-Isopropyl psoralene has two methyl groups, which decrease it's AChE inhibitory activity[69].

MISCELLANEOUS COMPOUNDS AS ACHE INHIBITORS

Table 10: Miscellaneous compounds as AChE inhibitors from plants

S.N.	Active constituent	Family	Plant name	Plant parts and extract	Class of compound	Ref no
1.	Bracteosin A Bracteosin B, Bracteosin C	Labiatae	*Ajuga bracteosa*	Whole plant, Ethanolic	Withanolide	71, 27
2.	Stioindosides, withaferinA	Solanaceae	*Withania somnifera*	Root		5
3.	Haloxysterols A, Haloxysterols B, Haloxysterols C, Haloxysterols D, 5a,8a-epidioxy-(24S)-ethylcholesta-6,9 (11), 22 (E) - triene -3b-ol , (24S)-ethylcholesta-7,9 (11), 22 (E)-triene-3b-ol, Lawsaritol , 24-ethyl-cholest-7-ene-3,5,6-triol , 24-ethylcholest-6-ene-3,5-diol	Chenopodiaceae	*Haloxylon recurvum*	Methanolic	Sterol	72
4.	Curcumin, bisdemethoxycurcumin and demethoxycurcumin	Zingiberaceae	*Curcuma longa* L.	Rhizome	Curcuminoid	73

Pereira *et al*. reported that phytochemical investigation of leave extract of *Jacaranda oxyphylla* provided three classes of substances and they are fatty compounds, sterols and triterpenes. Fatty compounds namely Butyl hexadecanoate, fatty alcohol, 2-(4-hydroxyphenyl) ethyl triacontanoate and sterols sitosterol-3-O-*β*-D-glucoside, 6'-palmitoyl-sitosterol-3-O-*β*-D-glucoside showed a significant acetylcholinesterase inhibitory activity with values between 60 to 77%[74]. T.O. Elufioye *et al* reported that leaf extract of *Pycnanthus angolensis* (Myristicaceae) inhibited both cholinesterase enzymes (AChE and BChE) and Two new bioactive compounds, (2E, 18E)-3,7,11,15,18-pentamethylhenicosa-2,18-dien-1-ol which is named as eluptol and [12-(4-hydroxy-3-methyl-oxo-cyclopenta-1,3-dien-1yl)-11-methyl-dodecyl](E)-3-(3,4-dimethylphenyl)prop-2-enoate which is named as omi-foate with remarkable cholinesterase inhibitory activity were isolated from the supernatant of the ethyl acetate

fraction (most active)[75]. F. Sezer Senol *et al* reported that the n-hexane:dichloromethane (1:1) root extract of *O. Nigricaule* (Boraginaceae) showed promising AChE inhibitory effect due to presence of shikonin derivatives from *O. Nigricaule*[76]. Chu *et al* reported that clausenamide (clau), a small molecule compound which is originally isolated from the traditional Chinese herbal medicine, *Clausenalansium* (family Rutaceae). Multiple experimental evidences proved that the (-)-clau (eutomer) induced improvement of cholinergic function is denoted by increasing the production and release of ACh and it doesn't block its hydrolysis. *In vivo* study showed increased ChAT activity in the neocortex, hippocampus and striatum of adult mice by oral administration of (-)-clau. It has been reported that (-)-clau reversibly inhibited AchE with a much lower potency than other available AchE inhibitors such as galanthamine[77]. Yilmaz *et al* reported that dichloromethane and methanolic extracts of *Nepeta obtusicrena* (aerial parts) and the isolated terpenoids showed high anticholinesterase activity and specially against acetylcholinesterase (AChE) enzyme. An abietane diterpene, obtusicrenone with a non-aromatic ring C exhibited high acetylcholinesterase inhibitory activity[78]. G. Rajakumar *et al* reported that the aqueous extract of *Millettia pinnata L.* flower showed acetylcholinesterase inhibitory activities with the IC50: 334.9±1.52 mg/ml. They also reported that AgNPs had a stronger inhibitory effect on both AChE and BChE than plant leaf extract[79]. Au nanoparticles and *D. kotschyi* (Labiatae) extract against human AChE and BChE were studied and the results showed that nanoparticles have a stronger anti-cholinesterase activity than those of plant extract[80]. Choon-Sheen Lai *et al* reported that extract of *S. palustris* (Burm.) Bedd. (Blechnaceae) frond extracts showed AChE inhibitory effects. MeOH extract from mature fronds shows the high anticholinesterase activity due to the presence of high content of flavonoids which contained a series of kaempferol glycosides. One of the compound, kaempferol 3-O-(600-O-E-p-coumaroyl)-b-glucopyranoside identified in this study which is reported to have strong AChE inhibitory actvitity[62].

CONCLUSION

In AD, Senile dementia, ataxia, myasthenia gravis, Parkinson's disease AchE inhibitors are having therapeutic applications. In the regulation of cognitive function cholinergic system is the most important neurotransmitter system involved. Herbal medicines are considered as big chemical libraries have been developed for the treatment of AD Many drugs in the market such as the plant alkaloids eg. Galantamine, efforts aim to treat Alzheimer's disease. Some traditional medicinal systems such as Ayurveda provide health maintenance as well as disease prevention over curative treatments. Hence in the future preclinical and clinical research into protective and preventive effects of herbals drugs should be carried out.

ABBREVIATIONS: AChE: Acetylcholinesterase, AD: Alzheimer's disease, ACh: Acetylcholine, BChE: Butyrylcholinesterase, ChAT: Choline acetyltransferase.

REFERENCES

1. Okano H, Hirano T, Balaban E. Learning and Memory. Proceedings of the National Academy of Sciences of United States of America 2000; 97:12403-12409
2. Zhang J. Memory Process and the Function of Sleep. Journal of Theoretics 2004; 6:1-7
3. Johnson S, Marro J, Torres JJ. Robust Short-Term Memory without Synaptic Learning. PLOS ONE 2013; 8:1-7
4. Brady TF, Konkle T, Alvarez GA, Oliva A. Visual long-term memory has a massive storage capacity for object details. Proceedings of the National Academy of Sciences of United States of America 2008; 105:14325-14329.
5. Suganthy N, Pandian SK, Devi KP. Cholinesterase inhibitors from Plants: Possible Treatment Strategy for Neurological Disorders- A Review. International Journal of Biomedical and Pharmaceutical Sciences 2009; 3:87-103
6. Raszewski G, Chwedorowicz R, Chwedorowicz A, Rothenberg KG**.** Homocysteine, antioxidant vitamins and lipids as biomarkers of neurodegeneration in Alzheimer's disease versus non-alzheimer's dementia. Annals of Agricultural and Environmental Medicine 2016; 23:193–196
7. Kumar B, Dwivedi C, Kesharwani S, Satapathy T, Tiwari SP, Yadav R, *et al*. Indian Herbal Medicines used for Treatment of Dementia: An Overview. World Journal of Pharmaceutical Research 2014; 3:344-382**.**
8. Paul S, Rajawat B, Tiwari R. Plants with nootropic activity: a review. World Journal of Pharmaceutical Research 2015; 4:591-607
9. Khan F. Dementia in India: it's high time to address the need!. Andhra Pradesh journal of Psychological Medicine 2011; 12:64-68
10. Rizzi L, Rosset I, Roriz-Cruz M. Global Epidemiology of Dementia: Alzheimer's and Vascular Types. Biomed Research International 2014; 3:1-8
11. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, *et al*. Global Prevalence of dementia: a Delphi consensus study. Lancet 2005; 366:2112–2117
12. Overshot R, Burns A. Treatment of dementia. Journal of Neurology Neurosurgery & Psychiatry 2005; 76:53–59.
13. Ernst E. The efficacy of herbal medicine-an overview. Fundamental & Clinical Pharmacology 2005; 19:405-409
14. Narayanaswamy N, Balakrishnan KP. Evaluation of some Medicinal Plants for their Antioxidant Properties. International Journal of Pharm Tech Research 2011; 3:381-385
15. Patel VS, Jivani NP, Patel SB. Medicinal Plants with Potential Nootropic Activity: A Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2014; 5:1-11
16. Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM, Acetylcholinesterase Inhibitors: pharmacology and toxicology. Current Neuropharmacology 2013; 11:315-335
17. Tripathi A, Srivastava UC. Acetylcholinesterase: A Versatile Enzyme of Nervous System, Annals of Neurosciences. 2008; 15:106-111.
18. Lionetto MG, Caricato R, Calisi A, Giordano ME, Schettino T. Acetylcholinesterase as a Biomarker in Environmental and Occupational Medicine: New Insights and Future Perspectives. BioMed Research International 2013; 2013:1-8
19. Getman DK, Eubanks JH, Camp S, Evans GA, Taylor P. The Human Gene Encoding Acetylcholinesterase Is Located on the Long Arm of Chromosome 7. American Journal of Human Genetics 1992; 51:170-177.
20. Houghton PJ, Ren Y, Howes MJ. Acetylcholinesterase inhibitors from plants and fungi. Natural Product Reports 2006; 23:181-199
21. Tougu V. Acetylcholinesterase: Mechanism of Catalysis and Inhibition. Current Medicinal Chemistry Central Nervous System Agents 2001; 1:155-170
22. Darvesh S, David A, Geula HC. Neurobiology of Butyrylcholinesterase. Nature Reviews Neuroscience 2003; 4:131-138.
23. Cokugras AN. Butyrylcholinesterase: Structure and Physiological Importance. Turkish Journal of Biochemistry 2003; 28:54-61.

24. Pohanka MM. Cholinesterases: A Target of Pharmacology and Toxicology. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2011; 155:219-230.
25. Sudha M, Sundaram RS, Annapondian V, Abhirama BR, Vazhayil BK, S. Gomathi S, Geethapriya C, *et al*. Natural Medicines Enhancing Neurite Growth in Central Nervous System Disorders: A Review. European Journal of Medicinal Plants 2016; 12:1-13
26. Hajiaghaee R, Akhondzadeh S. Herbal Medicine in the Treatment of Alzheimer's disease. Journal of Medicinal Plants 2012; 11:1-7
27. Ahmed F, Ghalib RM, Sasikala P, Ahmed KKM. Cholinesterase inhibitors from botanicals. Pharmacognosy Reviews 2013; 7:121-130
28. Khan I, Nisar M, Khan N, Saeed M, Nadeem S, Fazal-ur-Rehman, Ali F, *et al*. Structural insights to investigate Conypododiol as a dual cholinesterase inhibitor from *Asparagus adscendens*. Fitoterapia 2010; 81:1020-1025.
29. Adsersen A, Kjolbye A, Dall O, Jager AK. Acetylcholinesterase and butyrylcholinesterase inhibitory compounds from *Corydalis cava* Schweigg. & Kort. Journal of Ethnopharmacology 2007; 113:179-182.
30. Yangab ZD, Zhanga X, Duc J, Maa ZJ, Guoa F, Liad S, Yao XJ. An aporphine alkaloid from *Nelumbo nucifera* as an acetylcholinesterase inhibitor and the primary investigation for structure–activity correlations. Natural Product Research 2012; 26: 387–392.
31. Pal I, Dey P. A review on lotus (*Nelumbo Nucifera*) seed. International Journal of Science and Research 2015; 4:1659-1666.
32. Halldorsdottir ES, Jaroszewski JW, Olafsdottir ES. Acetylcholinesterase inhibitory activityof lycopodane typealkaloids from the Icelandic *Lycopodium annotinum* ssp. *alpestre*. Phytochemistry 2010; 71:149-57.
33. Rahman A, Parveen S, Khalid A, Farooq A, Choudhary MI. Acetyl and butyrylcholinesterase inhibiting triterpenoid alkaloids from *Buxus papillosa*. Phytochemistry 2001; 58:963-8.
34. Murray AP, Faraoni MB, Castro MJ, Alza NP, Cavallaro V. Natural AChE Inhibitors from Plants and their Contribution to Alzheimer's Disease Therapy. Current Neuropharmacology 2013; 11:388-413.
35. Park CH, Kim SH, Choi W, Lee YJ, Kim JS, Kang SS, Suh YH. Novel anticholinesterase and antiamnesic activities of dehydroevodiamine, a constituent of *Evodia rutaecarpa*. Planta Med 1996; 62:405-9.
36. Tang XC, Kindel GH, Kozikowski AP, Hanin I. Comparison of the effects of natural and synthetic huperzine: A on rat brain cholinergic function *in vitro* and *in vivo*. Journal of Ethnopharmacology 1994; 44:147-55
37. Williams P, Sorribas A, Melanie-Jayne R. Howes. Natural Products as a Source of Alzheimer's Drug Leads. Natural Product Reports 2011; 28:48-77
38. Satheeshkumar N, Mukherjee PK, Bhadra S, Saha BP. Acetylcholinesterase enzyme inhibitory potential of standardized extract of *Trigonella Foenum Graecum* L and its constituents. Phytomedicine 2010; 17:292-295.
39. Ahmad H, Ahmad S, Khan E, Shahzad A, Ali M, Tahir MN, Shaheen F, *et al.* Isolation: crystal structure determination and cholinesterase inhibitory potential of isotalatizidine hydrate from *Delphinium denudatum*. Pharmaceutical Biology 2016; 55:680-686
40. Karczmar A. Invited review: Anticholinesterases: Dramatic aspects of their use and misuse. Neurochemistry International 1998; 32:401-411.
41. Pereira DM, Ferreres F, Jorge MA, Oliveira JM, Gaspar L, Faria J, Valentao P, *et al*. Pharmacological effects of *Catharanthus Roseus* root alkaloids in acetylcholinesterase inhibition and cholinergic neurotransmission. Phytomedicine 2010; 17:646-652.
42. Kim SR, Hwang SY, Jang YP, Park MJ, Markelonis GJ, Oh TH, *et al*. Protopine from *Corydalis ternata* has anticholinesterase and antiamnesic activities. Planta Med 1999; 65:218-221
43. Ji HF, Shen L. A Potential Multipotent Natural Product to Combat Alzheimer's Disease. Molecules 2011; 16:6732-6740.
44. Tang J, Feng Y, Tsao S, Wang N, Curtain R, Wang Y. Berberine and Coptidis Rhizoma as novel antineoplastic agents: A review of traditional use and biomedical investigations. Journal Of Ethnopharmacology 2009; 126:5-17
45. Kim DK, Lee KT, Baek NI, Kim SH, Park HW, Lim JP, *et al*. Acetylcholinesterase inhibitors from the aerial parts of *Corydalis speciosa*. Archives of Pharmacal Research 2004; 27:1127-31.
46. Ng YP, Ip NY. Plant alkaloids as drug leads for Alzheimer's disease. Neurochemistry International 2015; 89:260-270.
47. Lopez S, Bastida J, Viladomat F, Codina C. Acetylcholinesterase inhibitory activity of some *Amaryllidaceae* alkaloids and *Narcissus* extracts. Life Sci 2002; 71:2521-9.
48. Rahman AU, Choudhary MI. Bioactive natural products as a potential source of new pharmacophores a theory of memory. Pure and Applied Chemistry 2001; 73:555-60
49. Khalid A, Zaheerul Haq, Ghayur MN, Fareeda Feroz F, Attaur Rahman, Gilanib AH, *et al*. Cholinesterase inhibitory and spasmolytic potential of steroidal alkaloids. The Journal of Steroid Biochemistry and Molecular Biology 2004; 92:477-84
50. Kivrak I, Duru ME, Ozturk M, Mercan N, Harmandar M, Topcu G. Antioxidant, anticholinesterase and antimicrobial constituents from the essential oil and ethanol extract of *Salvia potentillifolia*. Food Chemistry 2009; 116:470-9
51. Perry NS, Houghton PG, Theolad AE, Jenner P, Perry EK. *In vitro* inhibition of human erythrocyte acetylcholinesterase by *Salvia lavandulaefolia* essential oil and constituent terpenes. Journal of Pharmacy and Pharmacology 2000; 52:895-902.
52. Chung YK, Heo HJ, Kim EK, Kim HK, Huh TL, Lim Y, *et al*. Inhibitory effect of ursolic acid purified from *Origanum majorana* L on the acetylcholinesterase. Mol Cells 2001; 11:137-43.
53. Pattanaik J, Kumar Y, Khatri RS. *Acorus calamus* Linn. A herbal tonic for central nervous system. Journal of Scientific and Innovative Research 2013; 2:950-954.
54. Miyazawa M, Nakahashi H, Usami A, Matsuda N. Chemical composition, aroma evaluation, and inhibitory activity towards acetylcholinesterase of essential oils from *Gynura bicolor* DC. Journal of Natural Medicines 2016; 70:282-9.
55. Zhang J, Fan P, Zhu R, Li R, Lin Z, Sun B, *et al*. Marsupellins A−F, ent-Longipinane-Type Sesquiterpenoids from the Chinese Liverwort *Marsupella alpine* with Acetylcholinesterase Inhibitory Activity. Journal of Natural Products 2014; 77:1031-1036
56. Ji HF, Zhang HY. Theoritical evaluation of flavonoids as mulipotent agents to combat Alzheimer's disease. Journal of Molecular Structure :Theochem 2006; 767:3-9
57. Ozturk M, Kolak U, Topcu G, Oksuz S, Choudhary MI. Antioxidant and anticholinesterase active constituents from *Micromeria cilicica* by radical scavenging activity guided fractionation. Food Chemistry 2011; 126:31-8.
58. Jung M, Park M. Acetylcholinesterase inhibition by flavonoids from *Agrimonia pilosa.* Molecules 2007; 12:2130-9.
59. Ding X, Ouyang M, Liuand X, Wang RZ. Acetylcholinesterase Inhibitory Activities of Flavonoids from

the Leaves of *Ginkgo biloba* against Brown Planthopper. Journal of Chemistry 2013; 2013:1-4
60. Sancheti S, Sanchet S, Um BH, Seo SY. 1, 2, 3, 4, 6-penta-O-galloyl-β-d-glucose: A cholinesterase inhibitor from *Terminalia chebula*. South African Journal of Botany 2010; 76:285-228.
61. Kahraman C, Tatli II, Orhan IE, Akdemir ZS. Cholinesterase Inhibitory and Antioxidant Properties of *Verbascum mucronatum* Lam. and its Secondary Metabolites. Z. Naturforsch C 2010; 65:667-674.
62. Chear NJY, Khaw KY, Murugaiyah V, Lai CS. Cholinesterase inhibitory activity and chemical constituents of *Stenochlaena palustris* fronds at two different stages of maturity. Journal of Food and Drug Analysis 2016; 24:358-366.
63. Urbain A, Marston A, Queiroz EF, Ndjoko K, Hostettmann K, Xanthones from *Gentiana campestris* as new acetylcholinesterase inhibitors. Planta Med 2004; 70:1011-4.
64. Hung TM, Na M, Min BS, Ngoc TM, Lee I, Zhang X, *et al*. Acetylcholinesterase Inhibitory Effect of Lignans Isolated from *Schizandra chinensis*. Archives of Pharmacal Research 2007; 30:685-690
65. Tsai TH, Westly J, Lee TF, Chen CF, Wang LCH. Effects of Honokiol and magnolol on Acetylcholine release from rat hippocampal slices. Planta Medica 1995; 61:477-478
66. Howes MJR, Houghton PJ. Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function. Pharmacology, Biochemistry and Behavior 2003; 75:513-527.
67. Lee YK, Yuk DY, Kim TI, Kim YH, Kim KT, Kim KH, *et al*. Protective effect of the ethanol extract of *Magnolia officinalis* and 4-O-methylhonokiol on scopolamine-induced memory impairment and the inhibition of acetylcholinesterase activity. Journal of Natural Medicines 2009; 63:274-282.
68. Sung SH, Kang SY, Lee KY, Park MJ, Kim JH, Park JH, *et al*. (+)-α-Viniferin, a stilbene trimer from *Caragana chamlague*, inhibits acetylcholinesterase. Biological and Pharmaceutical Bulletin 2002; 25:125-7.
69. Ali MY, Jannat S, Jung HA, Choi RJ, Roy A, Cho JS. Anti-Alzheimer's disease potential of coumarins from *Angelica decursiva* and *Artemisia capillaris* and structure-activity analysis. Asian Pacific Journal of Tropical Medicine 2016; 9:103-111.
70. Lee MJH, Lee KT, Yang JH, Kim DK. Acetylcholinesterase Inhibitors from the Twigs of *Vaccinium oldhami*. Archives Pharmacal Research, 2004; 27:53-56.
71. Riaz N, Malik A, Rehman A, Muhammad P, Nawaz SA, Choudhary MI. Cholinesterase inhibiting withanolides from *Ajuga brateosa*. Chemistry & Biodiversity 2004; 1:1289-95.
72. Ahmed E, Nawaz SA, Malik A, Choudhary MI. Isolation and cholinesterase inhibition studies of sterols from *Haloxylon recurvum*. Bioorganic and Medicinal Chemistry Letters 2006; 16: 573 -580.
73. Ahmed T, Gilani AH. Inhibitory effect of curcuminoids on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia may explain medicinal use of turmeric in Alzheimer's disease. Pharmacology. Biochemistry and Behavior 2009: 91:554-559.
74. Pereira VV, Silva RR, Duarte LP. Chemical Constituents of *Jacaranda oxyphylla* and their Acetylcholinesterase Inhibitory and Antimicrobial Activities. Records of Natural Product 2016, 10:392-396.
75. Elufioye TO, Obuotor EM, Agbedahunsi JM, Adesanya SA. Cholinesterase inhibitory activity and structure elucidation of a newphytol derivative and a new cinnamic acid ester from *Pycnanthus angolensis*. Revista Brasileira de Farmacognosia 2016; 26:433-437.
76. Senol FS, Orhan IE, Ozgen U, Renda G, Bulut G, Guven L, *et al.* Memory-vitalizing effect of twenty-five medicinal and edible plants and their isolated compounds, South African Journal of Botany. 2016; 102:102-109
77. Chu S, Liu S, Duan W, Cheng Y, Jiang X, Zhu C, *et al.* The Anti-Dementia Drug Candidate, (-)-clausenamide, improves memory impairment through its multi-target effect. Pharmacology and Therapeutics 2016; 162:179-187.
78. Yilmaz A, Boga M, Topcu G. Novel terpenoids with potential anti-alzheimer activity from *Nepeta Obtusicrena*. Records of Natural Product 2016; 10:530-541
79. Rajakumar G, Gomathi T, Thiruvengadam M, Devirajeswari V, Kalpana VN, Chung IM. Evaluation of anti-cholinesterase, antibacterial and cytotoxic activities of green synthesized silver nanoparticles using from *Millettia Pinnata* flower extract. Microbial Pathogenesis 2017; 103:123-128
80. Dorosti N, Jamshidi F. Plant-mediated gold nanoparticles by *Dracocephalum Kotschyi* as anticholinesterase agent: Synthesis, characterization, and evaluation of anticancer and antibacterial activity. Journal of Applied Biomedicine 2016; 14:235-245

Cite this article as:

Purabi Deka *et al*. Some plants as a source of acetyl cholinesterase inhibitors: A Review. Int. Res. J. Pharm. 2017;8(5):5-13 http://dx.doi.org/10.7897/2230-8407.08565

Source of support: Nil, Conflict of interest: None Declared