Review Article

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

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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 process1. 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 shortest-lived memory and it lasts only milliseconds to a few seconds2. 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 minutes3,4. The long-term memory lasts anywhere from an hour to lifetime and it is normally believed to lack details2,5. But it is well confirmed that long-term memory can store a huge number of items4. 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 functioning6. 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 brain7. 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 life2,7,8. 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 respectively9. WHO projections suggested that about three-quarters of the population aged 60 or over will be living in developing countries by 202510. 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 ago13. 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 value14. 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 pathologies15.

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 activation16. 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 located17. 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. 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 site. 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 an acyl-enzyme and free choline. Then, by water molecule the acyl-enzyme undergoes nucleophilic attack, release acetic acid and regenerate the free enzymes. 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 20 Å 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. 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. 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 TcAChE. 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. 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.

Butyrylcholinesterase (BuChE)

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

### 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. AChE inhibitors can be divided into two groups: irreversible and reversible. Reversible inhibitors mostly have therapeutic applications. 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.

### HERBAL DRUGS AS CHOLINESTERASE INHIBITORS

For the discovery of new drugs, natural products remain a prolific source and these new drug leads even from Vedec period. Recent data proposed that 80% drug molecules are natural products (NPs) or natural compound inspired. 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. 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.

### 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.

### Table 1: Alkaloids as AChE inhibitors from plants

<table>
<thead>
<tr>
<th>S.N</th>
<th>Active constituent</th>
<th>Family</th>
<th>Plant name</th>
<th>Plant part and extract used</th>
<th>Class of compound</th>
<th>Ref no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lycorine, Tazetine, Crinine, 3-epi-hydroxybulbismerine, 2-demethoxy-montane, Galanthamine</td>
<td>Amaryllidaceae</td>
<td>Galanthus ikaireae</td>
<td>Bulb and Chloroform: methanol</td>
<td>Alkaloid</td>
<td>27</td>
</tr>
<tr>
<td>2.</td>
<td>Conypododiol</td>
<td>Asparagusaceae</td>
<td>Asparagus adscendens</td>
<td>Aerial parts and Ethanolic</td>
<td>Alkaloid</td>
<td>28</td>
</tr>
<tr>
<td>3.</td>
<td>Belbocainin, corydaline</td>
<td>Fumariaceae</td>
<td>Corydalis cava</td>
<td>Tubers and Methanolic</td>
<td>Alkaloid</td>
<td>29</td>
</tr>
<tr>
<td>4.</td>
<td>N-methylamisimoline</td>
<td>Nelumbonaceae</td>
<td>Nelumbo Nucifera</td>
<td>Leaves and Ethanolic</td>
<td>Alkaloid</td>
<td>30,31</td>
</tr>
<tr>
<td>5.</td>
<td>Annotine, Annotine, Annotine N-oxide, Lycodoline, Lycopodiumannum, Gnidiodine Lycodoline, Acrifline</td>
<td>Lycopodiaceae</td>
<td>Lycopodium annotinum</td>
<td>Aerial parts</td>
<td>Lycopodane-type alkaloid</td>
<td>32,27</td>
</tr>
<tr>
<td>6.</td>
<td>Buxakarachiamine, Buxakashmiramin,</td>
<td>Buxaceae</td>
<td>Buxas papillosa</td>
<td>Leaves and Ethanolic</td>
<td>Triterpenoid alkaloid</td>
<td>33,27</td>
</tr>
</tbody>
</table>
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 triad of AChE to form an ester in the urethane part 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 activity7.

Table 2: Indole alkaloids as AChE inhibitors from plants

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Active constituent</th>
<th>Family</th>
<th>Plant name</th>
<th>Plant parts used</th>
<th>Class of compound</th>
<th>Ref no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Physostigmine</td>
<td>Leguminosae</td>
<td>Physostigma venenomum</td>
<td>Seeds</td>
<td>Indole alkaloid</td>
<td>40, 37</td>
</tr>
<tr>
<td>2.</td>
<td>Rutecarpine and dehydroevodiamine</td>
<td>Rutaceae</td>
<td>Evodia rutacearpa (Juss.)</td>
<td>Aerial parts</td>
<td>Indole alkaloid</td>
<td>37</td>
</tr>
<tr>
<td>3.</td>
<td>Geissospermene</td>
<td>Apocynaceae</td>
<td>Geissospermum vellosii</td>
<td>Stem bark</td>
<td>Indole alkaloid</td>
<td>37</td>
</tr>
<tr>
<td>4.</td>
<td>Serpine</td>
<td>Apocynaceae</td>
<td>Catharanthus Roseus</td>
<td>Root</td>
<td>Indole alkaloid</td>
<td>41</td>
</tr>
<tr>
<td>5.</td>
<td>LegusinA</td>
<td>Papilionaceae</td>
<td>Desmodium pulchellum and D. gangeticum</td>
<td>Leaves and bark</td>
<td>Indole alkaloid</td>
<td>5</td>
</tr>
<tr>
<td>6.</td>
<td>Turbinatine and desoxycordifolie</td>
<td>Rutaceae</td>
<td>Chimarrhis turbinata</td>
<td>Leaf</td>
<td>Indole alkaloid</td>
<td>5</td>
</tr>
<tr>
<td>7.</td>
<td>Uleine</td>
<td>Apocynaceae</td>
<td>Himatanthus lancifolius,</td>
<td>Leaf</td>
<td>Indole alkaloid</td>
<td>34</td>
</tr>
</tbody>
</table>

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 alkaloids7.

Table 3: Isoquinoline alkaloids as AChE inhibitors from medicinal plants

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Active constituent</th>
<th>Family</th>
<th>Plant name</th>
<th>Plant parts used</th>
<th>Class of compound</th>
<th>Ref no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Protopine</td>
<td>Papaveraceae</td>
<td>Corydalis ternate</td>
<td>Tuber and methanolic</td>
<td>Isoquinoline alkaloid</td>
<td>42</td>
</tr>
<tr>
<td>2.</td>
<td>berberine</td>
<td>Huang Lian</td>
<td>Rizoma  Cortex</td>
<td>Aerial parts and methanolic</td>
<td>Isoquinoline alkaloid</td>
<td>43,44</td>
</tr>
<tr>
<td>3.</td>
<td>Corynoline</td>
<td>Papaveraceae</td>
<td>Corydalis incise</td>
<td>Aerial parts and methanolic</td>
<td>Isoquinoline alkaloid</td>
<td>5</td>
</tr>
<tr>
<td>4.</td>
<td>Palmatine, corynolide</td>
<td>Papaveraceae</td>
<td>Corydalis spectiosa</td>
<td>Aerial parts and methanolic</td>
<td>Isoquinoline alkaloid</td>
<td>45</td>
</tr>
</tbody>
</table>

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)6. Galanthamine binds at the base of the active site gorge of AChE which interacts with both coline –binding site as well as acyl binding pocket6. 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 cleft60.

Table 4: Steroidal alkaloids as AChE inhibitors from medicinal plants

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Active constituent</th>
<th>Family</th>
<th>Plant name</th>
<th>Plant parts used</th>
<th>Class of compound</th>
<th>Ref no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Galanthamine</td>
<td>Papaveraceae</td>
<td>Corydalis ternate</td>
<td>Tuber and methanolic</td>
<td>Steroidal alkaloid</td>
<td>34</td>
</tr>
<tr>
<td>2.</td>
<td>Huperzine A</td>
<td>Leucojum</td>
<td>Huperzia serrata</td>
<td>Whole plant, Methanolic</td>
<td>Steroidal alkaloid</td>
<td>35,7</td>
</tr>
<tr>
<td>3.</td>
<td>Stepharanine</td>
<td>Apocynaceae</td>
<td>Stepolarine</td>
<td>Whole plant, Methanolic</td>
<td>Steroidal alkaloid</td>
<td>36,7</td>
</tr>
<tr>
<td>4.</td>
<td>Diterpenoid alkaloids</td>
<td>Papaveraceae</td>
<td>Corydalis incise</td>
<td>Aerial parts, Methanolic</td>
<td>Diterpenoid alkaloids</td>
<td>39</td>
</tr>
</tbody>
</table>
**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.

**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 structure⁵⁶.

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<table>
<thead>
<tr>
<th>S.N.</th>
<th>Active constituent</th>
<th>Family</th>
<th>Plant name</th>
<th>Plant parts and extract</th>
<th>Class of compound</th>
<th>Ref no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Assoanine</td>
<td>Amaryllidaceae</td>
<td>Narcissus assoanus</td>
<td>Dormant Bulb and methanolic</td>
<td>Steroidal alkaloid</td>
<td>47, 27</td>
</tr>
<tr>
<td>2.</td>
<td>11-hydroxygalantamine</td>
<td>Amaryllidaceae</td>
<td>Narcissus poeticus</td>
<td>Dormant Bulb and methanolic</td>
<td>Steroidal alkaloid</td>
<td>47, 27</td>
</tr>
<tr>
<td>3.</td>
<td>Sanguinine</td>
<td>Amaryllidaceae</td>
<td>Eucharis grandiflora</td>
<td>Dormant Bulb and methanolic</td>
<td>Steroidal alkaloid</td>
<td>47, 27</td>
</tr>
<tr>
<td>4.</td>
<td>Epinigalantamine</td>
<td>Amaryllidaceae</td>
<td>Narcissus confuses, Narcissus perezchiscanoi, Narcissus leonensis, Narcissuslegionensis, Narcissus poeticus</td>
<td>Dormant Bulb and methanolic</td>
<td>Steroidal alkaloid</td>
<td>47, 27</td>
</tr>
<tr>
<td>5.</td>
<td>Homomoenjodaramine, moenjodaramine</td>
<td>Buxaceae</td>
<td>Buxus hyrcana</td>
<td>Steroidal alkaloid</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Sarsalignione, Vaganine,</td>
<td>Buxaceae</td>
<td>Sarcococca saligna</td>
<td>Steroidal alkaloid</td>
<td>48, 27</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Buxamine B</td>
<td>Buxaceae</td>
<td>Buxus hyrcana, Buxus papillosa</td>
<td>Steroidal alkaloid</td>
<td>48, 27</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Isoarocodine , Sarcorine , Sarcodine , Sarcocine , Alkaloid-C</td>
<td>Buxaceae</td>
<td>Sarcococca saligna</td>
<td>Whole plant and methanolic</td>
<td>Steroidal alkaloid</td>
<td>49, 27</td>
</tr>
</tbody>
</table>
GLYCOSIDE AS AChE INHIBITORS

Table 7: Glycoside as AChE inhibitors from plants

<table>
<thead>
<tr>
<th>S.N</th>
<th>Active constituent</th>
<th>Family</th>
<th>Plant name</th>
<th>Plant parts and extract</th>
<th>Class of compound</th>
<th>Ref no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Piperitone 7-O-b-D-glucoside</td>
<td>Lamiaceae</td>
<td>Micromeria cilicica</td>
<td>Aerial parts</td>
<td>Glycoside</td>
<td>57</td>
</tr>
<tr>
<td>2.</td>
<td>1,2,3,4,6-penta-O-galloyl-D-glucose</td>
<td>Combretaceae</td>
<td>Terminalia chebula</td>
<td>Leaves, Methanolic</td>
<td>Glycoside</td>
<td>60, 27</td>
</tr>
<tr>
<td>3.</td>
<td>Cynatoside B, Cynatoside A</td>
<td>Asclepiadaceae</td>
<td>Cynanchum atratum</td>
<td>Leaves, Methanolic</td>
<td>Pregnane glycoside</td>
<td>27</td>
</tr>
<tr>
<td>4.</td>
<td>Verbascoside</td>
<td>Scrophulariaceae</td>
<td>Verbascum munronatum</td>
<td>Leaves, Methanolic</td>
<td>Phenylethanoid glycosides</td>
<td>61</td>
</tr>
<tr>
<td>5.</td>
<td>Kaempferol 3-O-(600-O-E-p-coumaroyl)-b-glucopyranoside</td>
<td>Blechnaceae</td>
<td>Stenochlaena palastris</td>
<td>Fronds, Methanolic</td>
<td>Kaempferol glycoside</td>
<td>62</td>
</tr>
</tbody>
</table>

XANTHONE AS AChE INHIBITORS

Urbain et al reported that methanolic leaves extract of Gentiana campesi (family Gentianaceae) showed AChE inhibitory activity due to the presence of xanthones namely Bellidin, Bellidifolin, Bellidin 8-O-β-Bellidin 8-O-β glycyrryanoside (Norsertianolin) and Bellidifolin 8-O-β glycyrryanoside (swertianolin)\(^5\). In Bellidifolin absence of gluccopyranosyl moiety increases the AChE inhibitory activity than other xanthones which might be because of the steric factors or hydrophobicity. At it’s C-3 position, presence of methoxy group increases inhibitory 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 IC\(_{50}\) 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\(^5\).\(^4\)

Honokiol and Magnolol (lignans) were isolated from methanolic bark extract of Magnolia officinalis (family Magnoliaceae)\(^6\) and these biphenolic lignans (honokiol and magnolol) inhibited AChE activity in vitro, increased ChAT activity and hippocampal ACh release in vivo\(^5\).\(^6\). 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\(_{50}(12 \text{ nM})\)^\(^9\).

POLYPHENOLS AS AChE INHIBITORS

Table 8: Polyphenols as AChE inhibitors from plants

<table>
<thead>
<tr>
<th>S.N</th>
<th>Active constituent</th>
<th>Family</th>
<th>Plant name</th>
<th>Plant parts and extract</th>
<th>Class of compound</th>
<th>Ref no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Isoumacronulatol</td>
<td>Lamiaceae</td>
<td>Micromeria cilicica</td>
<td>Aerial parts</td>
<td>Isoflavone</td>
<td>57</td>
</tr>
<tr>
<td>2.</td>
<td>Sudachitin</td>
<td>Lamiaceae</td>
<td>Micromerian cilicica</td>
<td>Aerial parts</td>
<td>Polymethoxylated flavones</td>
<td>57</td>
</tr>
<tr>
<td>3.</td>
<td>Tiliroside, 3-Methoxy quercetin, Quercetin, Quercitrin</td>
<td>Rosaceae</td>
<td>Agrimonia pilosa</td>
<td>Whole plant, Methanolic</td>
<td>Flavonoid</td>
<td>58</td>
</tr>
<tr>
<td>4.</td>
<td>Sophoflavescenol, icarin, demethyl anhydrocirartin, 8-C-lavandurylkaempferol and kaempferol</td>
<td>Fabaceae</td>
<td>Sophora flavescens</td>
<td>Leaves, Methanolic</td>
<td>Flavonol</td>
<td>34</td>
</tr>
<tr>
<td>5.</td>
<td>quercetin-3-O-β-D-glucopyranoside, quercetin-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside</td>
<td>Ginkgoaceae</td>
<td>Ginkgo biloba</td>
<td>Leaves, Methanolic</td>
<td>Flavonol-O-glycosides</td>
<td>59</td>
</tr>
<tr>
<td>6.</td>
<td>Naringenin</td>
<td>Rutaceae</td>
<td>Citrus junos</td>
<td>Fronds, Methanolic</td>
<td>Flavanone</td>
<td>20</td>
</tr>
</tbody>
</table>
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 the bulky structure completely masks AChE as well as lowers the accessibility of substrate to AChE.

**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.

**MISCELLANEOUS COMPOUNDS AS AChE INHIBITORS**

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 stitosterol-3-O-β-D-glucoside, 6’-palmitol-stitosterol-3-O-β-D-glucoside showed a significant acetylcholinesterase inhibitory activity with values between 60 to 77% 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-pentamethylhenicosta-2,18-dien-1-ol which is named as eluptol and [12-(4-hydroxy-3-methyl-oxo-cyclopenta-1,3-dien-1-yl)]-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) F. Sezer Senol et al. reported that the n-hexane:dichloromethane (1:1) root extract of O. Nigricale (Boraginaceae) showed promising AChE inhibitory effect due to presence of shikonin derivatives from O. Nigricale. Chu et al. reported that clausenamide (clau), a small molecule compound from mature fronds shows the high anticholinesterase activity due to inhibition of both AChE and BChE. Hence in the future preclinical and clinical studies on plants show the health maintenance against human AChE and BChE were studied and the results showed that nanoparticles have a stronger anti-cho-linesterase activity than that of plant extract. 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 activity.

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 herbs drugs should be carried out.


REFERENCES


9. Khan F. Dementia in India: it's high time to address the need!. Andhra Pradesh journal of Psychological Medicine 2011; 12-68


59. Ding X, Ouyang M, Liuand X, Wang RZ. Acetylcholinesterase Inhibitory Activities of Flavonoids from

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