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An Approach to Alzheimer's Disease Treatment with Cholinesterase Inhibitory Activity from Various Plant Species

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Abstract: Alzheimer's disease rises with predictions of 115 million being affected by 2050 due to aging of the population, continuing lack of progress in identifying, effective treatment modalities and lack of predictive diagnostic techniques. Clinical treatment for this disease relies mostly on prolonging the availability of acetylcholine release into the neuronal synaptic cleft. Inhibition of acetylcholinesterase is the key enzyme which breakdowns acetylcholine, is considered as a promising strategy for the treatment Alzheimer's disease. An enormous source of acetylcholinesterase Inhibitors is provided by the abundance of plants in nature and also supportive for the development of new drug substances with amended targeting activity and reduced side effects. The present work organise a review of the literature on 350 species of medicinal plants that have been tested for acetylcholinesterase inhibitory activity which may be useful for researchers in their studies of natural product in the treatment of Alzheimer's disease.
Keywords: Plants, Acetylcholinesterase Inhibitors, Alzheimer's disease, Ellman's Method.

Introduction:

Alzheimer's disease was first described in 1906 by Alois Alzheimer who is a Bavarian neuropsychiatrist.[1] It is a complex, multifactorial, progressive, neurodegenerative disease primarily affecting the elderly population and is estimated to account for 50 – 60 % of dementia cases in persons over 65 years of age.[2] As the aged population grows, the number of individuals worldwide with ALZHEIMER'S DISEASE is expected to rise to 34 million in the next three decades, a dramatic increase from 7.3 million today.[3] Alzheimer's disease is characterised by a remarkable deficit in cholinergic neuronal transmission, particularly, affecting cholinergic neurons in the basal forebrain[4,5] Acetylcholine is an organic molecule liberated at the nerve endings as a neurotransmitter. It is produced by the synthetic enzyme choline acetyltransferase which uses acetyl coenzyme-A and Choline as substrates for the formation of Acetylcholine in specific cells known as cholinergic neurons. [6, 7]

The Acetylcholinesterase enzyme is an attractive target for the rational drug design and for the discovery of mechanism – based inhibitors because of its contribution in the hydrolysis of the neurotransmitter Acetylcholine. Acetylcholinesterase inhibitors are the most effective approach to treat the cognitive symptoms of Alzheimer's disease. [8,9.] The first acetylcholinesterase inhibitors specifically approved for the treatment of Alzheimer's disease was introduced in 1993 as 1, 2, 3, 4, - tetrahydro – 9 – aminoacridine (Tacrine)[10] Currently several Acetylcholinesterase inhibitors, such as Donepezil [11],Galantamine[12] , Rivastigmine [13] are available for the symptomatic treatment of patients with mild to moderate Alzheimer's disease. Although acetylcholinesterase inhibitors was the most widely used medication in Alzheimer's disease treatment, some

report propound that acetylcholinesterase inhibitors have inclement side effects such as anorexia, diarrhoea, fatigue, nausea, muscle cramps as well as gastrointestinal, cardiorespiratory, genitourinary and sleep disturbances[14]. This condition led the researchers in obtaining new acetylcholinesterase inhibitors with higher efficacy, improved bioavailability and reduced side effects, particularly from natural sources.

Acetylcholinesterase Inhibitors from Plants:

Plants have been used for the treatment of different kind of diseases from more than 3000 years. The biologically active natural compounds may have anticholinesterase activity and can be used as leader compounds for the synthesis of new drugs. The bioactive substances from fruits, vegetables and medicinal plants mainly includes indole, steroidal-piperidine-alkaloids, furanocoumarins, xanthones, flavonoids and diterpenes derivatives play a major role in the slowing of many pathogenesis and neurodegenerative disorders such as Alzheimer's disease[15,16,17]. Daily consumption of fresh vegetable reported in delaying of cognitive decline in older age.[18] Extracts of several medicinal plants have been reported to show acetylcholinesterase inhibitory activity. A summary of screening studies of these plants is provided in Table 1. This articles provides a summary of plants which have been reported to have acetylcholinesterase inhibitory activity along with the description of their family, scientific names, plant part, solvent used for extraction, percentage inhibition of acetylcholinesterase and the concentration at which the enzyme is inhibited.

Methodology for Determination of Ache Inhibitory Activity:

Several methods for screening of AChE inhibitory activity from natural resources has been reported based on Ellman's reactions[19]. The colorimetric method of Ellman et al. (1961) which is based on determining the amount of thiocholine released when acetylthiocholine or butyrylthiocholine is hydrolysed by AChE or BChE is widely used. The thiocholine released is quantified by its reaction with 5,5´-bisdithionitrobenzoic acid (DTNB), which produces a yellow 5-thio-2-nitrobenzoate anion[20].

The Ellman reaction for detecting AChE and BChE inhibitory activity has also been adapted for thin layer chromatography (TLC) plates. Samples are dotted on the plate before standard development, after which a solution of DTNB and acetylthiocholine iodide (ATCI) is sprayed until the plate is saturated. Thereafter the enzyme solution is sprayed on the plate and it is incubated for 5 min. A yellow coloration with white spots is indicative of inhibitory activity. This provides an extremely rapid method to screen large numbers of samples to discover new inhibitors of AChE[1] However; this method is known to give a number of false positive effects. To rule out such results, plates are first sprayed with DTNB, followed by a mixture of the enzyme and ATCI where the occurrence of white spots is indicative of false positive results[21, 1]. HPLC method for detection of AChE inhibition on immobilized AChE column[22] and HPLC with on-line coupled UV–MS–biochemical detection for AChE inhibitory activity [23] have also been reported.

Table. 1

Acetylcholinesterase inhibitory activity represented by plant extracts as determined by the microplate assay.

S.No	Species	Family	Parts Used	Solvent used for extraction	AChE Inhibition Activity (%)	Reference
1.	Acanthus ebracteatus Vahl.	Acanthaceae	Upper Part	Methanol	36.19±8.00(0.1mg/ml)	24
2.	Andrographis paniculata		Aerial	Water:Ethanol	222.41 (1µg/ml) (IC50)	25
3.	Alium sativum L.	Alliaceae	Rhizome	Methanol	3.02±3.14(0.1mg/ml)	24
4.	Crinum jagus	Amaryllidaceae	Leaves	Methanol	74.25±6.42 (42.5 µg/mL)	26
5.	Sternbergia candida		Whole plant	Ethanol	80.52±1.35(200µg/ml)	27
6.	Sternbergia clusiana		Whole plant	Ethanol	73.24±0.68(200µg/ml)	27
7.	Sternbergia fischeriana		Whole plant	Methanol	98.02±1.36	27
8.	Sternbergia subsp. Lutea		Whole plant	Methanol	N.E	27
9.	Crium moorel (B)		Bulbs	Ethanol	22.5 ± 6.5 (1 µg/ml) EC50	28
10.	Galanthus elwesii		Bulbs	Chloroform: Methanol (1:1)	73.18±1.01 (10 µg/ml)	29
11.	Narcissus tazetta subsp. tazetta L.		Bulbs	Chloroform: Methanol (1:1)	46.62±0.77 (10 µg/ml)	29
12.	Pancratium maritimum L		Bulbs	Chloroform: Methanol (1:1)	30.42±0.85 (10 µg/ml)	29
13.	Galanthus ikariae L.		Bulbs	Chloroform: Methanol (1:1)	75.56±0.99 (10 µg/ml)	29
14.	Leucojum aestivum L.		Bulbs	Chloroform: Methanol (1:1)	34.39±0.72 (10 µg/ml)	29
15.	Crinum moorei		Bulbs	Dichloromethane	2.9 µg/ml (IC50)	25
16.	Semecarpus anacardium Linn.	Anacardiaceae	Stem Barrk	Methanol	56.07±0.28(20µg/ml)	30
17.	Anacardium occidentale		Rhizomes	Methanol	4.6 (50 µg/ml)	31
18.	Harpephyllum caffrum		Stem barks	Methanol	0.02 (mg/ml) (IC50)	25
19.	Pistacia atlantica		Leaves	Water	0.87 µg/ml (IC50)	25
20.	Pistacia vera		Hull	Aqueous Methanol (1:1)	204.1 ± 6.33(µg/ml) (IC50)	32
21.	Spondias mombin		Roots bark	Methanol	64.77±2.73 (42.5 µg/mL)	26
22.	Centella asiatica Linn.	Apiaceae	Whole plant	Methanol	30.7±2.9 (0.1 mg/ml)	33
23.	Bunium persicum		Seeds	Methanol	16.8 (50 µg/ml)	31
24.	Chaerophyllum khorassanicum		Aerial parts	Methanol	N.E	31
25.	Cuminum cyminum		Seeds	Methanol	9.9 (50 µg/ml)	31
26.	Ferula oopoda		Aerial	Methanol	N.E	31

			parts			
27.	Ferulago angulata		Aerial parts	Methanol	5.3 (50 µg/ml)	31
28.	Foeniculum vulgare		Fruits	Methanol	N.E	31
29.	Heracleum persicum		Fruits	Methanol	6.5 (50 µg/ml)	31
30.	Levisticum officinale		Roots	Methanol	97.6 (50 µg/ml)	31
31.	Ferula assafoetida		Gum	Aqueous: Methanol (1:1)	281.3 ± 5.23(µg/ml) (IC50)	32
32.	Hollarhena floribunda		Roots bark	Methanol	22.39±1.21 (42.5 µg/mL)	26
33.	Tabernaemontana ddivaricata L.	Apocynaceae	Roots	Methanol	93.50±0.37(0.1mg/ml)	24
34.	Rauvolfia serpentina Linn.		Roots	Methanol	84.9±9.5 (0.1 mg/ml)	33
35.	Colocasta antiquorum (T)	Araceae	Tubers	Dichlorometnane	168.1±28.9 (µg/ml) EC50	28
36.	Acorus calamus Linn.		Rhizome	Methanol	43.79±7.2 (0.1 mg/ml)	33
37.	Caralluma socotrana	Asclepediaceae	Aerial parts	Chloroform	45.34 (0.2mg/ml)	34
38.	Aloe ferox (L)	Asphodelaceae	Leaves	Methanol	84.0±1.0 (µ g/ml) EC50	28
39.	Saussurea lappa C.B.Clarke.		Roots	Methanol	12.15±9.7 (0.1 mg/ml)	33
40.	Achillea eriophora		Aerial parts	Methanol	N.E	31
41.	Acantholepis orientalis		Aerial parts	Methanol	N.E	31
42.	Achillea wilhelmsii		Aerial parts	Methanol	0.1 (50 µg/ml)	31
43.	Acroptilon repens	Asteraceae	Aerial parts	Methanol	N.E	31
44.	Arctium lappa		Roots	Methanol	N.E	31
45.	Artemisia santolina		Aerial parts	Methanol	4.9 (50 µg/ml)	31
46.	Carthamus oxyacantha		Aerial parts	Methanol	N.E	31
47.	Cichorium intybus		Roots	Methanol	12.7 (50 µg/ml)	31
48.	Francoeuria undulate		Aerial parts	Methanol	3.1 (50 µg/ml)	31
49.	Gundelia tournefortii		Aerial parts	Methanol	N.E	31
50.	Matricaria aurea		Flowers	Methanol	N.E	31
51.	Outreya carduiformis	Asteraceae	Aerial parts	Methanol	12.3 (50 µg/ml)	31
52.	Sonchus asper		Aerial parts	Methanol	N.E	31
53.	Leontopodium alpinum Cass.		Roots	Dichloromethane	78.79 ± 2.59 (1 mg/ml)	35
54.	Biebersteinia multifida	Berberdaceae	Aerial parts & flowers	Methanol	2 (50 µg/ml)	31

55.	Berberis integrima		Roots	Methanol	80.2 (50 µg/ml)	31
56.	Markhamia tomentosa	Bignoniaceae	Stem bark	Methanol	40.61±4.01 (42.5 µg/mL)	26
57.	Bombax bromoposenze	Bombacaceae	Leaves	Methanol	14.33±1.91 (42.5 µg/mL)	26
58.	Ceiba pentadra		Stem bark	Methanol	18.99±0.42 (42.5 µg/mL)	26
59.	Cordia mixa	Boraginaceae	Fruits	Methanol	9 (50 µg/ml)	31
60.	Rapistrum rugosum L.		Flowers	Water	97.43±0.01 (10mg/ml)	36
61.	Cardaria draba		Aerial parts & flowers	Methanol	N.E	31
62.	Brassica alba	Brassicaceae	Seeds	Aqueous: Methanol (1:1)	84.3 ± 1.36 (µg/ml) (IC50)	32
63.	Brassica nigra		Seeds	Aqueous methanol (1:1)	135.0 ± 5.91(µg/ml) (IC50)	32
64.	Boswellia socotranao	Burseraceae	Resin	Chloroform	71.21 (0.2mg/ml)	34
65.	Boswellia elongatao		Resin	Chloroform	46.34 (0.2mg/ml)	34
66.	Buxus sempervirens	Buxaceae	N.M	Chloroform: Methanol	61.76±0.76(1mg/ml)	37
67.	Robinia Pseudoacacia	Caeselpiniaceae	N.M	Chloroform: Methanol	26.32±0.82(1mg/ml)	37
68.	Radix codonopsis		N.M	Ethanol	26.3(50µg/ml)	38
69.	Radix scutellariae		N.M	Ethanol	40.21(50µg/ml)	38
70.	Radix salviae miltiorrhizae		N.M	Ethanol	72.17(50µg/ml)	38
71.	Radix curcumae		N.M	Ethanol	25(50µg/ml)	38
72.	Rhizoma pineliae		N.M	Aqueous	9.74(50µg/ml)	38
73.	Radix et rhizoma rhei		N.M	Ethanol	80.97(50µg/ml)	38
74.	Radix paeoniae rubra		N.M	Aqueous	77.54(50µg/ml)	38
75.	Rhizoma acori tatarinowii	Campanulaceae	N.M	Ethanol	55.76(50µg/ml)	38
76.	Radix rehmanniae		N.M	Ethanol	23.77(50µg/ml)	38
77.	Radix et rhizoma glycyrrhizae		N.M	Ethanol	8.65(50µg/ml)	38
78.	Radix bupleuri		N.M	Ethanol	51.34(50µg/ml)	38
79.	Radix polygoni multiflori		N.M	Aqueous	59.88(50µg/ml)	38
80.	Radix polygalae		N.M	Aqueous	24.44(50µg/ml)	38
81.	Radix paeoniae alba		N.M	Aqueous	58.51(50µg/ml)	38
82.	Cannabis sativa		Seeds	Methanol	N.E	31
83.	Humulus lupulus	Cannabaceae	Flower	Aqueous: methanol (1:1)	369.6 ± 9.82(µg/ml) (IC50)	32
84.	Caryocar coriaceum Wittm.	Caryocaraceae	Seeds	Ethanol	63.4(500 μg/mL)	39
85.	Paronychia argentea	Caryophyllaceae	Aerial Part	Essential oil	49.5±1.0 (1mg/ml)	40
86.	Celastrus paniculatus Willd.	Celastraceae	Seeds	Methanol	23.13±2.3 (0.1 mg/ml)	33

87.	Licania tomentosa Benth	Chrysobalanaceae	Seeds	Ethanol	13.9(500 μg/mL)	39
88.	Licania rigida Benth		Seeds	Ethanol	52.4(500 μg/mL)	39
89.	Terminalia bellirica (Gaertn.) Roxb.	Combretaceae	Fruits	Methanol	39.68±8.15(0.1mg/ml)	24
90.	Combretum kraussii		Leaves	Ethyl Acetate	96±4.6 (1mg/ml)	41
91.	Trichilia dregeana		Bark	Ethanol	55±4.4 (1mg/ml)	41
92.	Terminalia chebula Retz.	Combretaceae	Whole fruit	Methanol	41.06±5.6 (0.1 mg/ml)	33
93.	Combretum molle		Roots bark	Methanol	24.72±2.32 (42.5 µg/mL)	26
94.	Terminalia chebulla		Fruits	Methanol	N.E	31
95.	Achillea phillea		Aerial parts	Methanol	9 (50 µg/ml)	31
96.	Carthamus tinctorius L.	Compositae	Flower	Methanol	30.33±9.22(0.1mg/ml)	24
97.	Pulicaria diversifolia		Aerial parts	Chloroform	41.23%(0.2mg/ml)	34
98.	Pulicaria stephanocarpa	Compositae	Leaves	Chloroform	61.43 (0.2mg/ml)	34
99.	Tragopogon carcifolius		Aerial parts	Methanol	4.7 (50 µg/ml)	31
100.	Connarus detersus Planch	Connaraceae	Seeds	Ethanol	91.9 (500 μg/mL)	39
101.	Convolvulus pilosellaefolius		Aerial parts	Methanol	10.4 (50 µg/ml)	31
102.	Convolvulus pluricaulis Choisy.	Convolvulaceae	Whole plant	Methanol	40.6±5.4 (0.1 mg/ml)	33
103.	Evolvulus alsinoides Linn.		Whole plant	Methanol	38.03±3.5 (0.1 mg/ml)	33
104.	Ipomoea asarifolia		Leaves	Methanol	0.12 (mg/ml) (IC50)	42
105.	Ipomea involucrata		Aerial part	Methanol	25.73±1.41 (42.5 µg/mL)	26
106.	Kalanchoe farinaceae	Crassulaceae	Leaves	Chloroform	45.21(0.2mg/ml)	34
107.	Kalanchoe brasiliensis Pers.		Leaves	Ethyl Acetate	0.16 (mg/ml) (IC50)	42
108.	Dendrosicycos socotrana	Cucurbitaceae	Bark	Methanol	31.95 (0.2mg/ml)	34
109.	Eureiandra balfourii		Tuber	Methanol	58.61 (0.2mg/ml)	34
110.	Juniperus communis subsp. Nana		Leaves	Ethanol	32.89±3.03(200µg/ml)	43
111.	Juniperus excelsa		Leaves	Water	42.28±2.43(200µg/ml)	43
112.	Juniperus foetidissima		Leaves	Water	22.71±0.04(200µg/ml)	43
113.	Juniperus oxycedrussubsp. Oxycedrus	Cupressaceae	Unripe fruit	Ethanol	19.88±3.32(200µg/ml)	43
114.	Juniperus sabina		Leaves	Ethanol	17.70±2.95(200µg/ml)	43
115.	Juniperus sabina		Fruit	Aqueous: Methanol (1:1)	379.9 ± 9.38(µg/ml) (IC50)	32
116.	Cyperus rotundus	Cyperaceae	Whole plant	Methanol	44.19±2.27(0.1mg/ml)	24
117.	Cystoseira indica	Cystosei	Whole	Methanol	11 mg/ml (IC50)	44

		raceae	plant			
118.	Cystoseira merica		Whole plant	Methanol	6 mg/ml (IC50)	44
119.	Padina australis	Dictyotaceae	Whole plant	Methanol	6.3 mg/ml (IC50)	45
120.	Discorea dumentorum	Dioscoreaceae	Tubers	Methanol	21.74±2.03 (42.5 µg/mL)	26
121.	Rhizoma dioscorea		N.M	Ethanol	20.73(50µg/ml)	38
122.	Diospyros rhodocalyx Kurz	Ebenaceae	Bark	Methanol	15.52±3.67(0.1mg/ml)	24
123.	Rhododendron ponticum Subsp.	Ericaceae	N.M.	Chloroform: Methanol	93.03±1.12(1mg/ml)	37
124.	Rhododendron luteum		N.M	Chloroform:Methanol	76.32±0.58(1mg/ml)	37
125.	Euphorbia antiquorum L.		Stem	Methanol	42.31±9.10(0.1mg/ml)	24
126.	Phyllanthus acidus (L.)Skeels		Leaves	Methanol	18.95±9.66(0.1mg/ml)	24
127.	Cephalocroton socotranus		Bark	Chloroform	51.1 (0.2mg/ml)	34
128.	Croton socotranus.		Bark	Chloroform	79.23 (0.2mg/ml)	34
129.	Emblica officinalis Gaertn.	Euphorbiaceae	whole fruit	Methanol	73.3±5.9 (0.1 mg/ml)	33
130.	Alchornea laxiflora		Leaves	Methanol	25.38±2.44 (42.5 µg/mL)	26
131.	Alchornea laxiflora		Roots bark	Methanol	31.47±1.07 (42.5 µg/mL)	26
132.	Alchornea laxiflora		Stem bark	Methanol	41.12±1.54 (42.5 µg/mL)	26
133.	Croton zambesicus		Leaves	Methanol	51.29±3.86 (42.5 µg/mL)	26
134.	Jatropha curcas		Leaves	Methanol	23.86±0.96 (42.5 µg/mL)	26
135.	Jatropha tangorensis		Leaves	Methanol	17.25±1.04 (42.5 µg/mL)	26
136.	Jatropha curcas L.		Leaves	Methanol	0.25 IC50 (mg/ml)	42
137.	Jatropha gossypiifolia L.		Leaves	Methanol	0.05 (mg/ml) (IC50)	42
138.	Euphorbia hebecarpa		Aerial parts & flowers	Methanol	N.E	31
139.	Vicia faba		N.G	Chloroform:Methanol	45.23±1.03 (1mg/ml)	37
140.	Glycine max		Seeds	Ethanol	68.4 (40mg/ml)	46
141.	Anadenanthera macrocarpa (Benth.)		Seeds	Ethanol	54.1(500 □g/mL)	39
142.	Parkia platycephala Benth.		Seeds	Ethanol	71.5(500 □g/mL)	39
143.	Piptadenia moniliformis Benth.	Fabaceae	Seeds	Ethanol	50.2(500 □g/mL)	39
144.	Albizia adianthifolia		Bark	Ethyl Acetate	61±5.1 (1mg/ml)	41
145.	Trigonella foenum graceum Linn.		Seeds	Methanol	6±0.9 (0.1 mg/ml)	33
146.	Amorpha fruticosa L.		Fruits	Methanol	48.86 ± 0.55 (0.17mg/ml)	47
147.	Alhagi camelorum		Aerial parts	Methanol	29.7 (50 µg/ml)	31
148.	Sophora alopecuroides		Aerial parts	Methanol	3 (50 µg/ml)	31
149.	Trigonella foenum		Seeds	Methanol	1.8 (50 µg/ml)	31

	graecum					
150.	Quercus infectoria		Galls	Methanol	21 .4 (50 µg/ml)	31
151.	Fumaria Vaillantii		N.M	Chloroform:Methanol	94.23±0.47 (1mg/ml)	37
152.	Fumaria capreolata		N.M	Chloroform:Methanol	96.89±0.17 (1mg/ml)	37
153.	Fumaria karalikii		N.M	Chloroform:Methanol	84.98±1.07 (1mg/ml)	37
154.	Fumaria asepala		N.M	Chloroform:Methanol	91.99±.70 (1mg/ml)	37
155.	Fumaria densiflora		N.M	Chloroform:Methanol	93.42±0.92 (1mg/ml)	37
156.	Fumaria flabellata	Fumariaceae	N.M	Chloroform:Methanol	92.14±1.01 (1mg/ml)	37
157.	Fumaria petteri subsp. Thuretii		N.M	Chloroform:Methanol	89.45±0.86 (1mg/ml)	37
158.	Fumaria macro carpa		N.M	Chloroform:Methanol	93.43±0.64 (1mg/ml)	37
159.	Fumaria cilicica		N.M	Chloroform:Methanol	88.03±0.65 (1mg/ml)	37
160.	Fumaria parviflora		N.M	Chloroform:Methanol	87.02±0.31 (1mg/ml)	37
161.	Fumaria Judaica		N.M	Chloroform:Methanol	96.47±0.63 (1mg/ml)	37
162.	Swertia longifolia Boiss.	Gentianaceae	Roots	Methanol	36.2±5.23 (300 µg/ml)	48
163.	Pelargonium graveolens	Geraniaceae	Aerial Part	Aqueous: Methanol (1:1)	196.9 ± 7.25(µg/ml) (IC50)	32
164.	Gracilaria corticata	Gracilariaceae	Whole plant	Methanol	9.5 mg/ml (IC50)	45
165.	G. salicornia		Whole plant	Methanol	8.7 mg/ml (IC50)	45
166.	Callophylum inophyllum	Guttiferaceae	Roots bark	Methanol	56.52±3.97 (42.5 µg/mL)	26
167.	Garcinia kola		Roots bark	Methanol	30.99±1.44 (42.5 µg/mL)	26
168.	Mammea harmandii Kosterm.	Guttiferae	flower	Methanol	33.63±8.00 (0.1mg/ml)	24
169.	Hypericum undulatum	Hypericaceae	Flowers	Ethanol	68.4±4.7 (0.5mg/ml)	40
170.	Crocus sativa	Iridaceae	Leaves	Methanol	N.E	31
171.	Juglans regia	Juglandaceae	External Shell	Aqueous: Methanol (1:1)	647.5 ± 8.61(µg/ml) (IC50)	32
172.	Vitex trifolia L.	Labiatae	Roots	Methanol	20.61±9.50 (0.1mg/ml)	24
173.	Salvia. albimaculata	Lamiaceae	Hedge	Petroleum Ether	89.4 ± 2.07 (1mg/ml)	49

174.	Salvia aucheri var. canescens	Hedge	Chloroform	64.5 ±1.03(1mg/ml)	49
175.	Salvia candidissima ssp. Occidentalis	Hedge	Chloroform	48.6 ± 5.13(1mg/ml)	49
176.	Salvia ceratophylla	Hedge	Chloroform	30.8 ± 5.2(1mg/ml)	49
177.	Salvia cyanescens	Hedge	Chloroform	80.2 ± 4.35(1mg/ml)	49
178.	Salvia cryptanhta	Hedge	Petroleum Ether	71.8 ± 2.62(1mg/ml)	49
179.	Salvia frigida	Hedge	Ethyl Acetate	59.5 ± 0.45(1mg/ml)	49
180.	Salvia forskahlei	Hedge	Ethyl Acetate	47.0±2.31 (1mg/ml)	49
181.	Salvia halophila	Hedge	Ethyl Acetate	36.1 ± 1.21 (1mg/ml)	49
182.	Salvia migrostegia	Hedge	Ethyl Acetate	37.1 ± 3.15 (1mg/ml)	49
183.	Salvia multicaulis	Hedge	Methanol	47.7 ± 3.58 (1mg/ml)	49
184.	Salvia sclarea	Hedge	Chloroform	55.3±0.98 (1mg/ml)	49
185.	Salvia syriaca	Hedge	Chloroform	66.9±2.49 (1mg/ml)	49
186.	Salvia verticillata ssp. amasiaca	Hedge	Petroleum Ether	45.6 ± 4.17 (1mg/ml)	49
187.	Lavandula angustifolia	Flower aerial parts	Essential oil	33.7±7.2 (0.5mg/ml)	40
188.	Lavandula pedunculata	Flower aerial parts	Essential oil	56.5±4.9 (0.5mg/ml)	40
189.	Melissa officinalis	Flower &Leaves	Essential oil	65.3±4.9 (1 mg/ml)	40
190.	Mentha suaveolens	Aerial Part	Essential oil	52.4±2.5 (1mg/ml)	40
191.	Salvia officinalis	Aerial Part	Essential oil	46.4±11.9 (0.5 mg/ml)	40
192.	Pycnostachys reticulata (L)	Roots	Methanol	28.8 ± 0.3 (µ g/ml) (EC50)	28
193.	Marrubium anisodon	Aerial parts	Methanol	27.7 (50 µg/ml)	31
194.	Mentha pulegium	N.M	Ethanol	534 ± 0.1 (µg/ml) (IC50)	50
195.	Mentha spicata	N.M	Water	721 ± 0.1(µg/ml) (IC50)	50
196.	Rosmarinus officinalis	N.M	Ethanol	219 ± 0.1 (µg/ml) (IC50)	50
197.	Thymus serpyllum	N.M	Ethanol	252 ± 0.1 (µg/ml) (IC50)	50
198.	Mentha longifolia	Aerial parts	Methanol	N.E	31
199.	Mentha piperita	Leaves	Methanol	4.2 (50 µg/ml)	31
200.	Nepeta crispa	Aerial parts	Methanol	6 (50 µg/ml)	31
201.	Nepeta saccharata	Whole the plant	Methanol	21.5 (50 µg/ml)	31
202.	Origanum majorana	Whole the plant	Methanol	7.9 (50 µg/ml)	31
203.	Otostegia persica	Aerial parts	Methanol	0.06 (50 µg/ml)	31
204.	Rosmarinus officinalis	Aerial parts	Methanol	N.E	31
205.	Salvia rhytidea	Whole the plant	Methanol	N.E	31

206.	Stachys lavandulifolia	Lamiaceae	Aerial parts	Methanol	7.4 (50 µg/ml)	31
207.	Teucrium polium		Aerial parts	Methanol	10 (50 µg/ml)	31
208.	Teucrium scordium		Aerial parts	Methanol	N.E	31
209.	Thymus serpyllum		Aerial parts	Methanol	N.E	31
210.	Zataria multiflora		Aerial parts	Methanol	8.2 (50 µg/ml)	31
211.	Zhumeria majdae		Leaves	Methanol	8.5 (50 µg/ml)	31
212.	Eremostachys laciniata		Whole the plant	Methanol	2.2 (50 µg/ml)	31
213.	Stachys inflate		Aerial parts	Methanol	5.2 (50 µg/ml)	31
214.	Laurus nobilis	Lauraceae	Leaves	Essential oil	51.3±1.7 (0.5mg/ml)	40
215.	Peltophorum pterocarpum	Leguminoceae	Stem bark	Methanol	68.85±3.53 (42.5 µg/mL)	26
216.	Tetrapleura tetraptera		Roots bark	Methanol	34.77±0.66 (42.5 µg/mL)	26
217.	Butea superba Roxb.		Roots Bark	Methanol	55.87±5.83(0.1mg/ml)	24
218.	Cassia fistula L.		Roots	Methanol	54.13±3.90 (0.1mg/ml)	24
219.	Derris scandens (Roxb.) Benth		stem Bark	Methanol	20.76±1.17 (0.1mg/ml)	24
220.	Mimosa pudica L.		Whole plant	Methanol	21.40±6.68 (0.1mg/ml)	24
221.	Pueraria candollei Wall. Ex Benth. Var		Roots	Methanol	25.26±8.28 (0.1mg/ml)	24
222.	Glycyrrhiza glabra Linn.		Roots	Methanol	35.01±4.6 (0.1 mg/ml)	33
223.	Senna alata (L.) Roxburgh.	Leguminosae	Leaves	Ethylacetate extract	0.08 (mg/ml)(IC50)	42
224.	Eremurus persicus		Aerial parts	Methanol	7(50 µg/ml)	31
225.	Linum usitatissimum		Seeds	Methanol	N.E	31
226.	Colchicum stevenii Kunth.	Liliaceae	seed	Methanol	8.07 ±3.69(200µg/ml)	51
227.	Colchicum variegatum L.		Seed	Methanol	35.50 ±2.26 (200µg/ml)	51
228.	Colchicum umbrosum Steven		Seed	Methanol	11.04 ±2.81 (200µg/ml)	51
229.	Colchicum balansae K. Perss.		Seed	Methanol	10.90 ±1.17(200µg/ml)	51
230.	Lycopodium clavatum	Lycopodiaceae	N.G	Chloroform:Methano	49.85±1.33 (1mg/ml)	37

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231.	Lawsonia inermis		Leaves	Methanol	8.6 (50 µg/ml)	31
232.	Punica granatum	Lythraceae	Fruit	Aqueous methanol (1:1)	408.2 ± 5.72(µg/ml) (IC50)	32
233.	Michelia Champaca L.		Leaves	Methanol	34.88±4.56(0.1mg/ml)	24
234.	Magnolia soulangiana Soul. Bod.	Magnoliaceae	Leaves and bark	Methanol	7.81 ± 1.22 µg/mL (IC50)	52
235.	Acridocarpus socotranus	Malpighiaceae	Leaves	Methanol	43.12% (0.2mg/ml)	34
236.	Malva silvestris		Leaves	Essential oil	28.1±2.9 (0.5mg/ml)	40
237.	Abutilon indicum L.		Whole plant	Methanol	30.66±1.06 (0.1mg/ml)	24
238.	Althaea officinalis		Flowers	Methanol	1.7 (50 µg/ml)	31
239.	Hibiscus gossypifolius	Malvaceae	Flowers	Methanol	0.5 (50 µg/ml)	31
240.	Malva sylvestris		Flowers	Methanol	1.5 (50 µg/ml)	31
241.	Tinospora cordifolia sMiers.		Stem Barrk	Methanol	77.74±0.38 (100µg/ml)	30
242.	Stephania suberosa Forman		Roots	Methanol	91.93±10.80 (0.1mg/ml)	24
243.	Tiliacora triandra (Colebr.) Diel		Roots	Methanol	42.29±2.89 (0.1mg/ml)	24
244.	Tinospora crispa (L.) Miers ex Hook.f.& Thomson	Menispermaceae	Stem	Methanol	18.04±6.99 (0.1mg/ml)	24
245.	Cissampelos owarensis		Aerial part	Methanol	19.59±0.81 (42.5 µg/mL)	26
246.	Acacia nilotica spp. kraussiana	Mimosaceae	Leaves	Ethanol	56±6.3 (1mg/ml)	41
247.	Acacia sieberiana var. woodii		Roots	Ethanol	62±4.1 (1mg/ml)	41
248.	Glinus oppositifolius (L.) A.DC.	Molluginaceae	Whole plant	Methanol	27.78±9.44 (0.1mg/ml)	24
249.	Ficus religiosa L.	Moraceae	stem Barrk	Methanol	52.60±2.91 (80µg/ml)	30
250.	Streblus asper Lour		Seeds	Methanol	30.51±4.21 (0.1mg/ml)	24

251.	Dorstenia gigas		Leaves	chloroform	65.12 (0.2mg/ml)	34
252.	Antiaris africana		Stem bark	Methanol	13.45±0.82 (42.5 µg/mL)	26
253.	Ficus carica		Leaves	Methanol	3.7 (50 µg/ml)	31
254.	Musa sapientum L.	Musaceae	Fruit Pulp	Methanol	29.14±4.73 (0.1mg/ml)	24
255.	Pycnanthus angolensis		Stem bark	Methanol	66.52±5.02 (42.5 µg/mL)	26
256.	Myristica fragrans	Myristicaceae	Seeds	Aqueous: Methanol (1:1)	1024. ±11.02(µg/ml) (IC50)	32
257.	Embelia ribes Burm.f.	Myrsinaceae	Roots	Methanol	72.63±0.69 (60µg/ml)	30
258.	syzygium cumini		Leaves	Ethyl Acetate	55.9±3.82 (µg/ml)(IC50)	53
259.	Syzygium aromaticum		Leaves	n-hexane	62.05±16.62 (µg/ml)(IC50)	53
260.	Syzygium polyanthum		Leaves	Methanol	47.3±3.54 (µg/ml)(IC50)	53
261.	Eucaliptus galbie	Myrtaceae	Leaves	Methanol	N.E	31
262.	Myrtus communis		Leaves	Methanol	20.4 (50 µg/ml)	31
263.	Nelumbo nucifera Gaertn.	Nelumbonaceae	stamen	Methanol	23.77±2.83 (0.1mg/ml)	24
264.	Nelumbo nucifera Gaertn.		flowers	Methanol	61.73±7.6 (0.1 mg/ml)	33
265.	Peganum harmala	Nitrariaceae	Aerial parts	Methanol	29.8 (50 µg/ml)	31
266.	Orchis mascula	Orchidaceae	Roots	Methanol	56.99 (250 µg/ml)	25
267.	Paeonia veitchii		Roots	Water	14 (µg/ml) (IC50)	25
268.	Paeonia lactiflora	Paeoniaceae	Roots	Ethanol	8 (µg/ml) (IC50)	25
269.	Corydalis solida subsp. Solida		N.M	Chloroform:Methanol	87.56±1.24 (1mg/ml)	37
270.	Glaucium corniculatum	Papaveraceae	N.M	Chloroform:Methanol	86.55±0.67 (1mg/ml)	37
271.	Corydalis solida ssp. slivenensis		Tuber	Water	96 (100 µg/ml)	25
272.	Corydalis intermedia	Papaveraceae	Tuber	Water	97 (100 µg/ml)	25
273.	Phytolacca americana L.	Phytolaccaceae	Leaves	Methanol	N.E	47
274.	Cedrus deodera		stem bark	Methanol	7.13±0.89 (0.1 mg/ml)	33
275.	Pinus halepensis	Pinaceae	Needle	Ethanol	60.15 (200 µg/ml)	25
276.	Piper nigrum L.		Seeds	Methanol	58.02±3.83 (0.1mg/ml)	24
277.	Piper interruptum Opiz	Piperaceae	Stem	Methanol	65.16±8.13 (0.1mg/ml)	24
278.	Plumbago indica L.	Plumbag	Roots	Methanol	30.14±3.28 (0.1mg/ml)	24

		inaceae				
279.	Limonium sokotranum		Leaves	Chloroform	43.23 (0.2mg/ml)	[34]
280.	Cymbopogon schoenanthus		Shoot	Methanol	0.23 ± 0.25 (mg/ml) (IC50)	[25]
281.	Cymbopogon jawarancusa	Poaceae	Whole plant	Methanol	72.36 (250 µg/ml)	[25]
282.	Triplaris gardnerianaWedd		Seeds	Ethanol	79.8 (500 □g/mL)	[39]
283.	Rheum ribes		Rhizomes	Methanol	72.4 (50 µg/ml)	[31]
284.	Ruprechtia apetala		Aerial	Ethanol	0.0779 (mg/ml) (IC50)	[25]
285.	Rheum palmatum	Polygonaceae	Roots and Rizhome	Ethanol	18 (µg/ml) (IC50)	[25]
286.	Fallopia multiflora		Roots	Water	13 µg/ml (IC50)	[25]
287.	Rheum officinale		Roots	Aqueous: Methanol (1:1)	341.7 ± 3.88(µg/ml) (IC50)	[32]
288.	Punica granatum Linn.	Punicaceae	Whole fruit	Methanol	62.4±5.3 (0.1 mg/ml)	[33]
289.	Clematis officinalis		Aerial parts	Methanol	18 (50 µg/ml)	[31]
290.	Nigella sativa	Ranunculaceae	Seeds	Methanol	N.E	[31]
291.	Zizyphus vulgaris		Fruit	Aqueous methanol (1:1)	24.37 ± 2.33(µg/ml) (IC50)	[32]
292.	Ziziphus joazeiro Mart		Seeds	Ethanol	49.4(500 □g/mL)	[39]
293.	Ziziphus spinachristi	Rhamnaceae	Leaves	Methanol	10.9 (50 µg/ml)	[31]
294.	Rhamnus prinoides		Roots	Water	0.201 (mg/ml) (IC50)	[25]
295.	Gelidiella acerosa	Rhodophyceae	Whole the plant	Hexane	54.18 ± 5.65 (487.80 µg/mL)	[54]
296.	Sanguisorba minor		Aerial Part	Ethanol	7.1±9.1 (1 mg/ml)	[40]
297.	Rosa damascene		Floret	Methanol	27.9 (50 µg/ml)	[31]
298.	Leucosidea sericea	Rosaceae	Stem	Dichloromethane	0.14 (mg/ml) (IC50)	[25]
299.	Rosa damascena		Flower	Aqueous Methanol (1:1)	93.1 ± 2.88(µg/ml) (IC50)	[32]
300.	Paederia linearis Hook. F		Whole plant	Methanol	29.31±6.39 (0.1mg/ml)	[24]
301.	Oldenlandia pulvinata		Aerial Parts	Chloroform	45.34 (0.2mg/ml)	[34]
302.	Morinda lucida		Leaves	Methanol	40.15±2.57 (42.5 µg/mL)	[26]
303.	Rubia tinctorium		Roots	Methanol	8.8(50 µg/ml)	[31]
304.	Galium odoratum		Whole plant	Hexane	53.1 (400 µg/ml)	[25]
305.	Morinda citrifolia		Fruit	Chloroform	78.11 µg/ml (IC50)	[25]
306.	Cinchona officinalis	Rubiaceae	Bark	Aqueous methanol (1:1)	187.6 ± 4.25(µg/ml) (IC50)	[32]
307.	Fructus alpiniae oxyphyllaa	Rubiaceae	N.M	Aqueous	21.3(50µg/ml)	[38]
308.	Fructus ligustri lucidi	Rubiaceae	N.M	Ethanol	24.52(50µg/ml)	[38]

309.	Ramulus uncariae cum	Rubiaceae	N.M	Aqueous	55.23(50µg/ml)	38
310.	Fructus schisandrae chinensis	Rubiaceae	N.M	Ethanol	5.76(50µg/ml)	38
311.	Fructus gardeniae	Rubiaceae	N.M	Ethanol	56.44(50µg/ml)	38
312.	Fructus corni	Rubiaceae	N.M	Aqueous	45.45(50µg/ml)	38
313.	Aegle marmelos (L.) Correa ex Roxb.		Fruit Pulp	Methanol	44.65±3.04 (0.1mg/ml)	24
314.	Citrus x aurantium		Flower	Aqueous methanol (1:1)	226.1 ± 7.41(µg/ml) (IC50)	32
315.	Citrus aurantium	Rutaceae	Flowers	Methanol	7.4 (50 µg/ml)	31
316.	Citrus sinensis		Fruits hull	Methanol	1.2 (50 µg/ml)	31
317.	Ruta graveolens		Whole plant	Hexane	34 (µg/ml) (IC50)	25
318.	Citrus aurantifolia		Fruit	Aqueous: Methanol (1:1)	19.57 ± 2.66(µg/ml) (IC50)	32
319.	Salix mucronata		Bark	Ethanol	82±3.9 (1mg/ml)	41
320.	Salix alba	Salicaceae	Bark	Aqueous: Methanol (1:1)	989.1 ± 4.29(µg/ml)(IC50)	32
321.	Salvadora persica	Salvadoraceae	Wood	Methanol	19 (50 µg/ml)	31
322.	Talisia esculenta (A. St.-Hil) Radlk		Seeds	Ethanol	61.24(500 □g/mL)	39
323.	Sapindus saponaria L.	Sapindaceae	Seeds	Ethanol	58.6(500 □g/mL)	39
324.	Mimusops elengi L.	Sapotaceae	flower	Methanol	32.81±5.36 (0.1mg/ml)	24
325.	Sargassum angosti-folium		Whole plant	Methanol	5.4 (mg/ml) (IC50)	45
326.	Sargassum oligocystum	Sargasseae	Whole plant	Methanol	2.5 (mg/ml) (IC50)	45
327.	Sargassum boveanum		Whole plant	Methanol	1 (mg/ml) (IC50)	45
328.	Scorphularia frigid	Scorophulariaceae	Aerial parts	Methanol	2.9 (50 µg/ml)	31
329.	Bacopa monniera (Linn.) Pennell		Whole plant	Methanol	15.15±0.97 (0.1 mg/ml)	33
330.	Verbascum kermanensis	Scrophulariaceae	Leaves	Methanol	2.7 (50 µg/ml)	31
331.	Verbascum songaricum		Aerial parts	Methanol	N.E	31
332.	Withania Somnifera Dunal.		Roots	Methanol	74.37±0.38 (100µg/ml)	30
333.	Capsicum frutensis		Leaves	Methanol	10.34±0.83 (42.5 µg/mL)	26
334.	Hyoscyamus senecionis	Solanaceae	Aerial parts & flowers	Methanol	3.5 (50 µg/ml)	31
335.	Solanum dulcamara		Fruits	Methanol	4.8 (50 µg/ml)	31
336.	Witheringia coccoloboides	Solanaceae	Whole plant	Methanol	220.68 (mg/l) (IC50)	25

337.	Solanum leucocarpum		Whole plant	Methanol	204.59 (mg/l) (IC50)	25
338.	Camellia sinensis	Theaceae	Leaves	Aqueous: Methanol (1:1)	5.96 + 0.73 (µg/ml)(IC50)	32
339.	Falcaria vulgaris	Umbelliferaceae	Aerial parts	Methanol	6.6 (50 µg/ml)	31
340.	Coriandrum sativum		Leaves	Methanol	36.25±5.3 (0.1 mg/ml)	33
341.	Apium graveolens	Umbelliferae	Leaves	Methanol	4.7 (50 µg/ml)	31
342.	Urtica dioica	Urticacea	Aerial parts	Methanol	2.9 (50 µg/ml)	31
343.	Nardostachys jatamansi DC.		Rhizome	Methanol	69.24±0.15 (100µg/ml)	30
344.	Nardostachys jatamansi DC.	Valerianaceae	Rhizome	Methanol	83.83±9.2 (0.1 mg/ml)	33
345.	Valeriana wallichii DC.		Roots	Methanol	8.82 ± 0.7 (0.1 mg/ml)	33
346.	Alpinia officinarum	Zingiberaceae	Rhizomes	Methanol	0.4 (50 µg/ml)	31
347.	Zingiber officinale		Rhizomes	Methanol	0.6 (50 µg/ml)	31
348.	Kaempfera parviflora		Rhizome	Ethanol	20.64 (µg/ml) (IC50)	25
349.	Tribulus terrrestris	Zygophyllaceae	N.M	Chloroform:Methanol	37.89±0.77 (1mg/ml)	37
350.	Zygoophyllum fabago		N.M	Chloroform:Methanol	13.25±0.45 (1mg/ml)	37

(**N.M**-Not Mentioned, **N.E**-No Effect)

Results and Discussion:

Active Phytoconstituents isolated from plants having anticholinesterase inhibitory activity

The first known AChE inhibitor was physostigmine and alkaloid isolated from physostigmine Venenosum Balf. Which was used in therapy before the discovery of Ach as neurotransmitter. Rivastigmine ,Cymserine,Neostigmine and Pyridostigmine are synthetically derived analogues developed from Physostigmine. Some of the alkaloids isolated from plants includes, isoquinoline alkaloids Berberine and Groenlandicine from Chinese Rhizoma coptidis, Tubocurarine alkaloids from chondrodn tomentosum, Galantamine from Galanthus nivalis. Geissospermine indole-indoline alkaloid from Geissospermum vellosii Allem and sesquiterpene alkaloid from Huperzia serrata Thumb. Methoxsalen, a furanocumarin also known as Xanthotoxin was extracted from Poncirus trifoliate(l.) Raf. Pomiferin a prenylated isoflavone from Maclura pominifera (Raf.). Mansonone Napthoquinone from Thespesia populnea (L.) Withanolides steroidal lactone Monoterpenoids from Withania somnifera (L.) and Eucalyptus globules Labill. Bellidifolin, Xanthones isolated from Gentiana campestris L[55]

Plant belonging to families Acanthaceae, Alliaceae, Amaryllidaceae, Anacardiaceae, Apiaceae, Apocynaceae, Araceae, Asclepediaceae, Asphodelaceae, Asteraceae, Asteraceae, Berberdaceae, Bignoniaceae, Bombacaceae, Boraginaceae, Brassicaceae, Burseraceae, Buxaceae, Caeselpiniaceae, Campanulaceae, Cannabaceae, Caryocaraceae, Caryophyllaceae, Celastraceae, Chrysobalanaceae, Combretaceae, Compositae, Concolvulaceae Connaraceae, Crassulaceae, Cucurbitaceae, Cupressaceae, Cyperaceae, Cystoseiraceae, Dictyotaceae, Dioscoreaceae, Ebenaceae, Ericaceae, Euphorbiaceae, Fabaceae, Fumariaceae, Gentianaceae, Geraniaceae, Gracilariaceae, Guttiferaceae, Guttiferae, Hypericaceae, Iridaceae, Juglandaceae, Labiatae, Lamiaceae, Lauraceae, Leguminoceae, Liliaceae, Lamiaceae, Lycopodiaceae, Lythraceae, Magnoliaceae, Malpighiaceae, Malvaceae, Menispermaceae, Mimosaceae, Molluginaceae, Moraceae, Musaceae, Myristicaceae, Myrsinaceae, Myrtaceae, Nelumbonaceae, Nitrariaceae, Orchidaceae, Paeoniaceae, Papaveraceae, Phytolaccaceae, Pinaceae, Piperaceae, Plumbaginaceae, Poaceae, Polygonaceae, Punicaceae,

Ranunculaceae, Rhamnaceae, Rhodophyceae, Rosaceae, Rubiaceae, Rutaceae, Salicaceae Salvadoraceae, Sapindaceae, Sapotaceae, Sargasseae, Scorophulariaceae, Solanaceae Theaceae, Umbelliferaceae, Urticacea, Valerianaceae, Zingiberaceae and Zygophyllaceae have been reported to have Acetylcholinesterase inhibitory activity.

Conclusion:

In conclusion, these findings suggest that these plants which were reported to have anticholinesterase activity may have favourable pharmacological profile in the treatment of Alzheimer 's disease. Since Acetylcholine plays a vital role in cognitive function including learning and memory and is evident that the anticholinesterse activity has memory enhancing properties. Clinical significance of these plants can be evolved by studying their active phytoconstituients, toxicity studies and further mechanistic studies are to be assessed and explored.

Conflict of interest statement

We declare that we have no conflict of interest.

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