INTRODUCTION

Alzheimer’s disease (AD) is a progressive neuro-degenerative disorder associated with memory impairment and cognitive deficit. It is characterized by low levels of acetylcholine in the brain of AD patients. According to the cholinergic hypothesis, the inhibition of acetylcholinesterase (AChE), an enzyme that catalyzes acetylcholine hydrolysis, increases the levels of acetylcholine in the brain, thus improving cholinergic functions in AD patients. Furthermore, although the general consensus concludes that AChE inhibitors (AChEi) can alleviate AD symptoms, they neither delay nor reverse the disease progress. Most of the drugs currently available for the treatment of AD are AChEi: tacrine (1), donepezil (2), rivastigmine (3) and galanthamine (4), all of which have limited effectiveness and some kind of side effect [1]. Tacrine (1) and donepezil (2), both from synthetic origin, were the first drugs approved for the treatment of cognitive loss in AD patients by US-FDA in 1993 and 1996, respectively. Rivastigmine (3) was approved in 2000 (US-FDA) and was designed from the lead compound physostigmine, a natural AChEi alkaloid. Galanthamine (4), a natural alkaloid first obtained from Galanthus spp. was approved by US-FDA in 2001. Huperzine A (5), an alkaloid found in Huperzia spp., is an AChEi commercialized as a dietary supplement for memory support and it is used to treat AD symptoms in China. This alkaloid has been thoroughly studied with promising results yielded particularly from the evaluation of cognitive performance of animals as well as from studies on its efficacy, tolerance and safety.

Taking into account that inhibitors 3, 4 and 5 are related to natural products and that AChEi are an important therapeutic strategy for the treatment of AD, many research groups have focused their studies on naturally-occurring compounds from plants as potential sources of either new or more effective AChEi. These studies led to the discovery of an important number of secondary metabolites as well as plant extracts, both of which are characterized by their ability to inhibit AChE. On the other hand, the fact that a significantly relevant number of research papers has been recorded in this field during the last decades can be clearly attributed to the development of colorimetric methods which allow a rapid and facile screening of a large number of samples. Ellman’s method is the most widely used for the detection of AChEi, even in complex mixtures, and for the quantification of anti-AChE inhibitory activity [2-6].

Several reviews on the newly discovered AChEi obtained from plants, fungi and marine organisms have also been published over the last years [7-10]. The majority of these AChEi belong to the alkaloid group, including indole, isoquinoline, quinolizidine, piperidine and steroidal alkaloids. On the other hand, several non-alkaloidal and potent AChEi have been obtained from natural sources, including terpenoids, flavonoids and other phenolic compounds. Interestingly, although literature demonstrates to be rich in the study on AChEi obtained from plants, this issue keeps on being the center of attention for research as confirmed by the increasing number of studies published every year. Therefore, the purpose of this review is to provide a comprehensive summary of the literature, particularly that published during 2006-2012 (1st semester) on plant-derived compounds, plant extracts and essential oils.

Keywords: Alzheimer’s Disease, acetylcholinesterase inhibitors, secondary metabolites, plant extracts, essential oils.

Abstract: As acetylcholinesterase (AChE) inhibitors are an important therapeutic strategy in Alzheimer’s disease, efforts are being made in search of new molecules with anti-AChE activity. The fact that naturally-occurring compounds from plants are considered to be a potential source of new inhibitors has led to the discovery of an important number of secondary metabolites and plant extracts with the ability of inhibiting the enzyme AChE, which, according to the cholinergic hypothesis, increases the levels of the neurotransmitter acetylcholine in the brain, thus improving cholinergic functions in patients with Alzheimer’s disease and alleviating the symptoms of this neurological disorder. This review summarizes a total of 128 studies which correspond to the most relevant research work published during 2006-2012 (1st semester) on plant-derived compounds, plant extracts and essential oils found to elicit AChE inhibition.

Keywords: Alzheimer’s Disease, acetylcholinesterase inhibitors, secondary metabolites, plant extracts, essential oils.
Natural AChE Inhibitors from Plants and their Contribution

Current Neuropharmacology, 2013, Vol. 11, No. 4

389

extracts and essential oils which have been reported to inhibit AChE. Readers interested not only in previous findings but also in synthetic/semisynthetic AChEi or natural AChEi of fungal, marine or microbial origin are recommended to see the above-mentioned reviews [i.e. 7-10]. For the sake of brevity and in order to focus our attention on the most relevant findings, only those research papers reporting quantified results (IC50 and/or percentage of inhibition at a given concentration) were included. Extracts or essential oils with IC50 > 0.5 mg/ml were considered weakly active and were therefore not taken into account in the present review. With a few exceptions, only molecules with IC50 < 50 M have been considered. Furthermore, unless otherwise stated, those results on AChE inhibition included in the present review refer to in vitro assays carried out with AChE from electric eel.

ALKALOIDS WITH AChE INHIBITORY ACTIVITY

The quinoline alkaloids 3-hydroxy-2,2,6-trimethyl-3,4,5,6-tetrahydro-2H-pyrano[3,2-c] quinoline-5-one (6), ribalinine (7) and methyl isoplatydesmine (8) isolated from the aerial parts of *Skimmia laureola* (Rutaceae) were found to be linear mixed inhibitors of AChE with *K*<sub>i</sub> = 110.0, 30.0 and 30.0 M, respectively [11]. These alkaloids were also observed to evidence butyrylcholinesterase (BChE) inhibition.

On the other hand, of the several alkaloids that were isolated from the active extracts of *Esenbeckia leiocarpa* (Rutaceae), leptomerine (9) and kokusaginine (10) with IC50 values of 2.5 and 46 M, respectively, were observed to elicit AChE inhibitory activity [12]. The isolation of skimmianine (11), a furoquinoline alkaloid with very low AChE inhibitory activity, was also reported by the same authors. This alkaloid was observed in another Rutaceae, *Zanthoxylum nitidum*, exhibiting a moderate AChE inhibitory activity (IC50 = 8.6 µg/ml) [13].

*Nelumbo nucifera* is a well-known medicinal plant belonging to the Nelumbonaceae family which was studied due to its therapeutic potential [14]. N-methylasimilobine (12), an aporphine alkaloid with an IC50 = 1.5 µg/ml which was found to be a non-competitive inhibitor, was recently isolated from this plant [15]. In a random screening, two extracts of *Beilschmiedia* species were observed to exhibit AChE inhibition and a phytochemical study of *B. alloiophylla* and *B. kunstleri* revealed the presence of several alkaloids with IC50 values ranging between 2.0 and 10.0 M [16]. The most potent AChEi were found to be 2-hydroxy-9-methoxyaporphine (13), laurotetanine (14), liriodenine (15) and oreobeiline (16) (IC50 = 2.0-5.0 M), with anti-AChE activity comparable to huperzine A (IC50 = 1.8 µM). A significant AChE inhibitory activity was also observed in...
secoboldine (17), boldine (18), asimilobine (20) and 3-methoxynordomesticine (21) (IC$_{50}$ = 8.4 - 10.0 µM).

Research on plants from the genus Corydalis (Papaveraceae) which are used for the treatment of memory dysfunction in folk medicine reported the presence of benzylisoquinoline alkaloids with anti-AChE activity [7]. The ethanolic extract obtained from the tuber of C. turtschaninovii previously found to elicit AChE inhibition was selected to carry out a chemical study which led to the isolation of the isoquinoline alkaloids stylopine (22), epiberberine (23), pseudodehydrocorydaline (24), pseudocopsitine (25) and pseudoberberine (26). In the assay with mouse brain cortex as a source of AChE enzyme, the IC$_{50}$ values obtained for each of these alkaloids were 15.8, 6.5, 8.4, 4.3 and 4.5 µM, respectively [17]. In addition, alkaloids 25 and 26, the two most active compounds, were found to elicit anti-amnesic activity [17, 18]. Alkaloids with benzylisoquinoline skeleton from Corydalis species having aromatic methylenedioxy groups and a quaternary atom of nitrogen were observed to show the strongest AChE inhibition [7, 17, 18]. In a more recent work, six protoberberine alkaloids 23, 27 - 31, were identified in rhizomes of Coptis chinensis which are traditionally used in Chinese medicine for the treatment of various diseases. Coptidis rhizomes and their alkaloids were reported to have cognitive-enhancing and neuroprotective effects and the analysis of the anti-AChE activity of these alkaloids showed that the IC$_{50}$ values of berberine (27), palmatine (28), jateorrhizine (29), coptisine (30) and groenlandicine (31) ranged between 0.44 and 0.80 µM while that of epiberberine (23) was slightly higher (IC$_{50}$ = 1.07 µM) [19]. Of these alkaloids, compounds 27, 30 and 31 were observed to have an aromatic methylenedioxy group. In this study groenlandicine (31) and berberine (27) were found to be the most active as BChE inhibitors and epiberberine (23) was observed to significantly inhibit β-secretase (BACE1) [19].

The alkaloids (+)-canadaline (32) and (+)-canadine (33), both isolated from Corydalis cava and with an IC$_{50}$ = 20.1
and 12.4 μM, respectively, were observed to elicit a moderate inhibitory activity when tested with AChE from human blood [20].

On the other hand, *Stephania venosa* (Menispermaceae), a Thai medicinal plant, was found to show a high AChE inhibitory activity. The ethanolic extract of *S. venosa* was subjected to bioassay-guided fractionation to identify AChEi [21]. The following moderately active quaternary protoberberine alkaloids could be isolated: stepharanine (34), cyclanoline (35) and N-methyl stepholidine (36) with IC₅₀ values of 14.10, 9.23 and 31.30 μM, respectively. A similar fractionation approach was followed to identify the compounds responsible for AChE inhibition in *Chelidonium majus* (Papaveraceae) [22]. Three active constituents were identified, namely 8-hydroxydihydrochelerythrine (37), 8-hydroxydihydrosanguinarine (38) and berberine (27). Compounds 37 and 38, with no previous record as AChEi, were found to elicit significant anti-AChE activity with an IC₅₀ = 0.61 and 1.37 μM, respectively.

Taspine (39) was isolated from the alkaloid-enriched extract obtained from *Magnolia x soulangiana* (Magnoliaceae) [23]. This alkaloid was found not only to show a dose-dependent and long-lasting inhibitory effect on AChE (IC₅₀ = 0.33 μM) but also to be more potent than galanthamine (IC₅₀ = 3.2 μM) although its inhibitory activity is comparable to that of tacrine (IC₅₀ = 0.22 μM). Similar observations were obtained when the *in vitro* assay was performed with human AChE (IC₅₀ = 0.54 μM). Compound 39 resulted to be inactive against BChE, acting as a selective AChEi.

*Catharanthus roseus* (Apocynaceae) is a plant mainly known as a source of vincristine and vinblastine, two alkaloids found in its leaves and appreciated as anticancer compounds. Several other compounds with biological importance can be also found in *C. roseus*. For example, the alkaloid serpentine (40), isolated from the roots of this plant, was reported to be a potent *in vitro* AChEi (IC₅₀ = 0.775 μM) compared with physostigmine (IC₅₀ = 6.45 μM) [24].

A bioassay-guided fractionation from the stems of *Ervatamia hainanensis* (Apocynaceae), a plant used in traditional Chinese medicine, allowed the isolation of several monoterpenoid indole alkaloids, some of them showing a potent AChE inhibitory activity [25]. For example, coronaridine (41) and voacangine (42), differing from each other only by the methoxy group attached to the aromatic ring, were observed to have an IC₅₀ = 8.6 and 4.4 μM, respectively, these values being similar to that of galanthamine (3.2 μM). On the other hand, 10-hydroxycoronaridine (43) was found to evidence a reduced AChE inhibition (IC₅₀ = 29 μM), which was attributed to the introduction of a hydroxyl group to the aromatic ring. The indole alkaloids coronaridine (41) and voacangine (42), both detected in the stalks of *Tabernaemontana australis* (Apocynaceae), had been formerly identified as AChEi but no inhibition values were reported [26].

The genus *Tabernaemontana* is known for the wide variety of unusual bioactive indole alkaloids it produces. Among them, the bisindole alkaloids isolated from *T. divaricata* roots are an interesting example of new structures with potent AChE inhibitory activity. The crude alkaloid extract obtained from the root of *T. divaricata* was found to yield four bisindole alkaloids 44 - 47 [27]. The analysis of AChE inhibition revealed that 19,20-dihydratabernamine (44) and 19,20-dihydroyvanahanine A (45) strongly inhibit AChE, with an IC₅₀ = 0.227 and 0.071 μM, respectively, thus showing that they are significantly more active than galanthamine (IC₅₀ = 0.594 μM). The fact that inhibition was found to be higher for compound 45 than for compound 44 suggests that the introduction of a carboxethoxy group at C16' increases the enzymatic inhibition. In addition, taking into account that conodurine (46) and tabernaegentiane (47)
were found to show no activity in AChE, it was suggested that the substitution at C11' and C12' is relevant for AChE inhibitory activity [27].

Uncaria rhynchophylla (Rubiaceae) is a Chinese medicine herb used to treat epilepsy. The alkaloid fraction from U. rhynchophylla is known for its antiepileptic and neuroprotective effects. Geissoschizine methyl ether (48), a strong AChEi, as well as six other weakly active alkaloids were recently isolated from this herb [28]. The active compound 48 was observed to inhibit AChE in a reversible and non-competitive way with an IC$_{50}$ = 3.7 µg/ml.

The study of AChE inhibitory activity of Brazilian apocynacea Himatanthus lancifolius, commonly known as “agoniada”, led to the identification of active extracts in this plant and allowed the isolation of uleine (49), an active indole alkaloid, at a high concentration in the alkaloid fraction. The IC$_{50}$ value observed for this alkaloid was 0.45 µM [29].

As to the Amaryllidaceae family, phytochemical research conducted in the last decades on this family revealed several alkaloids with moderate or potent inhibition of AChE [3, 7, 30]. In the search of new natural sources of galanthamine and other Amaryllidaceae alkaloids with anti-AChE activity, bulbs and leaves of Hippeastrum papilio collected in the South of Brazil were studied. Galanthamine (4), the already known alkaloids narwedine (50), haemanthamine (51), 11-hydroxyvittatine (52), 8-O-demethylmaritidine (53) and vittatine (54) as well as the new alkaloid 11β-hydroxygalanthamine (55) were all isolated and of all of them galanthamine was obtained in significant amounts [31]. Compound 55 was observed to elicit AChE inhibition as other galanthamine-type alkaloids do, with an IC$_{50}$ = 14.5 µM. Furthermore, because habranthine, epimer of 55, was observed to have an anti-AChE activity similar to that of galanthamine, it was concluded that β configuration at C11 is unfavorable for the interaction with AChE [3, 31]. Other potent AChEi, such as N-allylnorgalanthamine (56) and N-14-methylallylnorgalanthamine (57), were isolated from Leucojum aestivum, an amaryllidacea used for the industrial extraction of galanthamine [32]. N-alkylated galanthamine derivatives 56 and 57 were isolated together with galanthamine (4), epinorgalanthamine (58), narwedine (50) and lycorine (59), from the mother liquors obtained after the industrial production of galanthamine. Alkaloids 56 and 57, with IC$_{50}$ values of 0.18 and 0.16 µM, respectively, resulted to be ten times more potent AChEi than galanthamine (IC$_{50}$ = 1.82 µM).

The chemical investigation of Galanthus rizehensis, a wild-growing species from Turkey, allowed the isolation of two new Amaryllidaceae alkaloid N-oxides, incartine N-oxide (60) and lycorine N-oxide (61) and seven
known alkaloids namely, 1-acetyl-β-carboline (62), incartine (63), N-trans feruloyltyramine (64), lycorine (59), O-methylnorbelladine (65), vittatine (54) and 11-hydroxyvittatine (52) [33]. The potential of these alkaloids as AChEi was analyzed but only incartine N-oxide (60) was observed to elicit a moderate inhibitory activity (IC\(_{50}\) = 34.50 \(\mu\)M), incartine (63) was observed to be weakly active (IC\(_{50}\) = 106.97 \(\mu\)M) and the other alkaloids were found to be inactive. In a bioassay-guided fractionation of an active extract obtained from bulbs of Nerine bowdenii, the Amaryllidaceae alkaloid undulatine (66) was identified as the most active component of the alkaloid fraction, with an IC\(_{50}\) = 37 \(\mu\)M [34].

Although benzylphenethylamine alkaloids were considered to belong exclusively to the Amaryllidaceae, some of them have been found to belong to other families [35]. A new example of this exception was found through the chemical investigation of Hosta plantaginea (Liliaceae) [36]. Seventeen benzylphenethylamine alkaloids, including five new alkaloids, 67-71, along with twelve known compounds [7-deoxy-trans-dihydrornarciclasine, O-methyllycorine, albomaculine, haemanthamine, O-demethylhaemanthamine, 8-O-demethylnaritidine, haemanthidine, yemenine C, lycorine, pseudolycorenine, ungeremine (72) and norsanguinine (73)] were obtained. Some of these alkaloids were analyzed to determine whether they are AChEi or not. Ungeremine (72) (IC\(_{50}\) = 3.85 \(\mu\)M), norsanguinine (73) (IC\(_{50}\) = 1.43 \(\mu\)M) and 8-demethoxy-10-O-methylhostasine (69) (IC\(_{50}\) = 2.32 \(\mu\)M) were all found to be potent AChE inhibitors.
After the isolation of the potent AChEi huperzine A (5) from *Huperzia serrata* (Lycopodiaceae), several plants belonging to the genus *Lycopodium* have been investigated in an attempt to find alkaloids with unusual skeletons that could have AChE inhibitory activity [7, 8, 37]. Five new *Lycopodium* alkaloids, 11α-hydroxyfawcettidine (74), 2α,11α-dihydroxyfawcettidine (75), 8α,11α-dihydroxyfawcettidine (76), 2β-hydroxylycothunine (77) and 8α-hydroxylycothunine (78), with the fawcettimine skeleton were isolated from *L. serratum*, along with three known alkaloids, lycothunine (79), serratine (80) and serratamine (81) [38]. AChE inhibitory activity was analyzed for the *L. serratum*-derived lycoposerramine-H (82) previously isolated from *L. serratum* [39] and for compounds 74, 75, 78. Alkaloids 75 and 82 were observed to inhibit AChE with an IC₅₀ = 27.9 and 16.7 μM, respectively, while 74 and 78 were observed to show no anti-AChE activity. In another study, three new alkaloids (83 - 85) were isolated from *L. carinatum*, a species collected in Malasya [40]. Carinatumin A (83) and B (84) were observed to inhibit AChE from bovine erythrocytes with an IC₅₀ = 4.6 and 7.0 μM, respectively, whereas carinatumin C (85) was observed to show no inhibition (IC₅₀ > 100 μM). Alkaloids 83 and 84 were observed to exhibit an AChE inhibitory activity similar to that of huperzine A and huperzine B (IC₅₀ = 0.8 and 8.0 μM). Alkaloids from *L. casuarinoides* were also isolated and characterized, of which lycoparin C (88) and lycoparin B (87), both having a carboxylic acid at C-15 and one or two N-methyl groups, were found to show no inhibitory activity.

As to *Sarcococca* and *Buxus* species (Buxaceae), they are known to produce steroidal alkaloids, some of which were observed to evidence strong AChE inhibition [7, 42, 43]. New steroidal alkaloid AChEi from *S. saligna* and *S. hookeriana* were recently found. In the case of *S. saligna*, the study—which was a continuation of previous research [44, 45]– of the bioactive steroidal alkaloids of this species allowed the isolation of five new compounds (89-93) and two already known bases (94 and 95) [46]. The new alkaloids 5,14-dehydro-Nₓ-demethylsarcodagine (89), 14-dehydro-Nₓ-demethylsarcodagine (90), 16-dehydrosarcorine (91), 2,3-dehydrosarsalignone (92) and 14,15-dehydrosarcoravin D (93), as well as the known compounds sarcovagene C (94) and salignarine C (95) were analyzed as anti-AChE agents. Only 91, 92 and 95 were observed to exhibit significant AChE inhibition (IC₅₀ = 12.5, 7.0 and 19.7 μM, respectively). Compounds 89 - 92, 94 and 95 were also found to elicit strong and selective BChE inhibition [46]. The bioassay-guided chemical investigation of *S. hookeriana* allowed the isolation of two new pregnane-type steroidal alkaloids, hookerianamide H (96) and hookerianamide I (97) together with the known alkaloids *N*ₓ-methyllepipachyamine D (98), sarcovagine C (94) and dictyophepine (99) [47]. Compounds 94, 96, 97, 98 and 99 were tested for their inhibitory properties towards AChE and all of them were found to elicit significant inhibitory activity (IC₅₀ = 2.9 – 34.1 μM) as well as a potent anti-BChE activity (IC₅₀ = 0.3 – 3.6 μM). Further studies on *S. hookeriana* yielded two new 5α-pregnan-type steroidal alkaloids, hookerianamides J (100) and K (101) [48]. Furthermore, eight known steroidal alkaloids, hookerianamide H (96) and hookerianamide I (97), chonemorphine (102), N-methyllepipachyamine A (103), epipachysamine-E-5-en-4-one (104), vagenine A (105), 2,3-dehydrosarcoravin G (92) and sarcovagene C (94), were isolated and characterized. Alkaloids 94, 100, 101, 102, 103 and 104 were analyzed as AChEi. Compounds 100, 101, 102

---

**Chemical Structures:**

- 67: R₁= H, R₂= OCH₃
- 68: R₁= H, R₂= H
- 69: R₁= CH₃, R₂= H
- 70: R₁= CH₃, R₂= OCH₃
- 71
- 72
- 73
- 83
- 84
- 85
- 86: R₁=COOH, R₂=R₃=CH₃
- 87: R₁=COOH, R₂=CH₃, R₃=H
- 88: R₁=CH₂OH, R₂=R₃=H
and 103 were observed to inhibit AChE moderately (IC\textsubscript{50} 22.1 - 48.5 \textmu M) while 104 and 94 were found to be more active inhibitors (IC\textsubscript{50} 9.9 and 8.1 \textmu M, respectively).

Phytochemical research on Buxus hyrcana allowed the identification of several Buxus alkaloids with cholinesterase inhibitory activity [43, 49]. Three new triterpenoidal alkaloids, namely 17-oxo-3-benzoylbuxadine (106), buxhyrcamine (107) and 31-demethylcyclobuxoviridine (108) along with sixteen known compounds, all tested as AChEi, were isolated and characterized in a recent study on B. hyrcana collected from Iran [50]. Weak AChE inhibitory activity was observed for \textit{N}\textsubscript{b}-dimethylcyclobuxoviricine (109), papilozine \textit{C} (110), cyclobuxophylline \textit{O} (111) and arborea-1,9(11)-dien-3-one (112) (IC\textsubscript{50} 35.4 - 47.9 \textmu M). In the same \textit{in vitro} assay, 17-oxo-3-benzoxybuxadine (106), buxhyrcamine (107), homomoenjodaramine (113), buxmicrophylline \textit{F} (114), buxrugulosamine (115), moenjodaramine (116) and \textit{N}\textsubscript{20}-formyl-buxaminol \textit{E} (117) were observed to show moderate AChE inhibition (IC\textsubscript{50} 17.6 - 25.5 \textmu M) while spirofornabuxine (118) was found to elicit a strong AChE inhibitory activity (IC\textsubscript{50} = 6.3 \textmu M).

The crude methanolic extract of B. natalensis, a plant used to improve memory in the elderly by traditional healers in South Africa, was found to elicit AChE inhibition (IC\textsubscript{50} =
The phytochemical study of this extract yielded seven compounds 119 - 125 which were found to show either moderate or strong AChE inhibition [51]. The alkaloids $O^5$-natafuranamine (119), $O^{10}$-natafuranamine (120), cyclonataminol (121) and 31-demethylbuxaminol (122) were isolated and characterized for the first time while buxaminol A (123) was isolated for the first time as a natural product. Buxafuranamide (124) and buxalongifolamidine (125) were already known compounds. Compounds 119, 120 and 124 were observed to exhibit a significantly higher AChE inhibitory activity compared to the rest, with IC$_{50}$ values of 3.0, 8.5, and 14.0 μM, respectively. Compounds 121, 122, 123 and 125 were observed to be less effective as AChEi (IC$_{50}$ = 22.9 – 30.2 μM).

The bulbs of *Fritillaria* species (Liliaceae) which are known to be a traditional medicinal herb called “Beimu” in
China are used as an antitussive, antiasthmatic and expectorant agent. In the past, in a chemical study carried out on alkaloids from *F. imperialis* bulbs new steroidal alkaloids with weak AChE inhibition and great selectivity towards BChE were identified [52]. Thus, taking into account this previous study, the bulbs from five *Fritillaria* species were studied and their alkaloids were identified and evaluated as cholinesterase inhibitors. Eighteen alkaloids were isolated and their effects on human whole blood cholinesterase were assayed. Results showed that *N*-demethyl-puqietinone (126) from *F. puqiensis*, hupeheninoside (127) from *F. hupehensis*, ebeiedinone (128) from *F. ebeiensis var. purpurea*, yibeinoside A (129) from *F. pallidiflora* and chuanbeinone (130) from *F. delavayi* showed good AChE inhibition, with IC$_{50}$ values of 6.4, 16.9, 5.7, 6.5 and 7.7 M, respectively. However, all of them were weaker AChEi than galanthamine (IC$_{50}$ = 1.9 M). Compounds 127, 128, 129 and 130 were found to be stronger inhibitors on plasma BChE than galanthamine, the positive control [53].

In addition, the following steroidal alkaloids: conessine (131), isoconessimine (132), conessimin (133), conarrhinin (134) and conimin (135) were isolated in a bioassay-guided fractionation from the seeds of *Holarrhena antidysenterica* (Apocynaceae), a common Tibetan drug [54]. Compounds 131, 133, 134 and 135 were identified as active constituents against AChE. Conessimin (133) was found to be the strongest AChE inhibitor with an IC$_{50}$ = 4 M whereas conessine (131), conarrhinin (134) and conimin (135) were found to be moderate AChE inhibitors (IC$_{50}$ = 21 - 28 M). These findings indicate that the elimination of the N-methyl group of pyrrolidine moiety induces a significant increase of activity while the cleavage of either one or two N-methyl groups at C-3 position reduces the inhibitory potency. Compound 133 was selected for a kinetic study through which it was demonstrated that its AChE inhibitory activity is both reversible and non-competitive. Molecular docking simulations of these compounds with AChE helped to understand their interactions with AChE and were consistent with the experimental results obtained [54].

### NON-ALKALOIDAL COMPOUNDS WITH AChE INHIBITORY ACTIVITY

In spite of the fact that the majority of the most potent inhibitors known to date are alkaloids, several non-alkaloidal
AChEi from the plant kingdom and with different structural characteristics (terpenoids, sterols, flavonoids and phenolic compounds, etc) have been recognized as promising lead compounds as anti-AD agents [7-10]. Until 2006 only a few diterpenoids demonstrated to inhibit AChE [7]. However, further recent research has reported a larger number of compounds belonging to this group with the ability to exert either moderate or strong AChE inhibitory activity. In addition, a new cassane diterpene named niloticane (136) was isolated from the ethyl acetate bark extract of Acacia nilotica subsp. kraussiana (Fabaceae), a plant used in African traditional medicine [55]. Niloticane (136) was found to show an AChE inhibitory activity similar to that of the positive control galanthamine (IC50 = 4 and 2 μM, respectively). In addition, one new (137) and six known (138 - 143) labdane-type diterpenoids were identified as AChE inhibitors present in an active extract obtained from Leonurus heterophyllus (Lamiaceae) by bioassay-guided fractionation [56]. Anti-AChE activity in 137 – 143 was analyzed in rat brain cortex as a source of AChE enzyme. Leoheteronin A (141) and leopersin G (143), both having a 15,16 epoxy group, were observed to be strong inhibitors with IC50 values of 11.6 and 12.9 μM, respectively. The new compounds leoheteronin F (137) and leoheteronin D (142) were found to show moderate inhibition with IC50 values of 16.1 and 18.4 μM, respectively. Leoheterin (138), hispanone (139) and galeopsin (140), all having a furan ring at the side chain, were found to be weakly active (IC50 = 38.5 - 42.7 μM).

Asparagus adscendens (Asparagaceae) is a medicinal plant traditionally used as a nerve tonic and remedy for memory impairments in Pakistan. Conypodiol (144), which was isolated from the chloroform fraction of the methanolic extract of A. adscendens, was found to elicit AChE and BChE inhibition with an IC50 = 2.17 and 11.21 μM, respectively [57]. This dual cholinesterase inhibitor was also observed to show potential as a bivalent ligand in molecular docking studies. Four non-competitive AChEi 145
- 148 were obtained in the chemical investigation of *Ajuga bracteosa* (Lamiaceae), another medicinal plant from Pakistan [58]. The diterpenoid dihydroajugapitin (148) was found to be the most active against AChE with an IC₅₀ = 14.0 μM. Compared to compound 148, lupulin A (147), clerodinin A (146) and dihydroclerodin (145) were observed to be less efficient inhibitors (IC₅₀ = 19.2, 26.5 and 35.2, respectively) and diterpenoids 145 - 148 were observed to elicit BChE inhibition. These findings indicate that the presence of a methoxy group at C-15 increases cholinesterase inhibitory potential.

From the methanolic extract of *Haloxylon recurvum* (Chenopodiaceae), a plant used in Pakistan for the treatment of several neuronal disorders, four new C-24 alkylated sterols 149 – 152 and five known sterols 153 – 157 were isolated [59]. Compounds 149 – 157 were analyzed as AChEi and were found to inhibit AChE in a concentration-dependent manner acting as non-competitive inhibitors. Haloysterol B (150) and haloysterol C (151), whose IC₅₀ values were 0.89 and 1.0 μM, respectively, were found to be the most active AChE inhibitors. Their inhibitory activity was observed to be similar to that of galanthamine (IC₅₀ 0.5


Cholinesterase inhibitors, of which the most active resulted to be 6-geranyl-3,3',5,5',7-pentahydroxy-4'-methoxyflavane (164), 6-geranyl-3',5',5',7-tetrahydroxy-4'-methoxyflavane (165) and diplacone (166), which were observed to show mixed-type inhibition of human AChE with IC50= 15.6, 22.9 and 7.2 M, respectively [63]. In addition, the fact that these compounds were also observed to elicit significant BChE inhibition makes them interesting as potential dual inhibitors.

The flavonols present in Sophora flavescens (Fabaceae) were studied for several biological activities relevant for AD. Sophoflavescenol (167), icarinin (168), demethylanhydro-icaritin (169), 8-C-lavandulylkaempferol (170) and kaempferol (171) were all found to be good AChE inhibitors, with IC50 values of 8.37, 6.47, 6.67, 5.16 and 3.31 M, respectively [64]. Compounds 167–171 were also found to elicit significant BChE and BACE1 inhibition.

The methanol extract from roots of Morus lhou (Moraceae), a polyphenol-rich plant, was found to yield nine flavonoids (172–180) of which eight showed AChE inhibition [65]. A new flavone, 5'-geranyl-4'-methoxy-5,7,2'-trihydroxyflavone (172), was identified as the most potent inhibitor (IC50 = 10.95 M). 5'-geranyl-5,7,2',4'-tetrahydroxyflavone (173), kuwanon U (174), kuwanon E (175), morusin (176), neocyclomorusin (179) and kuwanon C (180) were all observed to be moderate AChE inhibitors (IC50 = 16.21 - 36.4 M) and morusinol (177) was observed to be weakly active (IC50 = 173.49 M). C-3 prenylated flavones 176, 178, 179 and 180 were found to be noncompetitive inhibitors whereas those unsubstituted at C-3 172–175 were mixed inhibitors. Flavonoids 172–180 were also found to inhibit BChE [65].

On the other hand, three potent AChEi were obtained from Broussonetia papyrifera, another plant belonging to the Moraceae family. From the ethanolic extract of the roots of B. papyrifera which was found to elicit cholinesterase inhibitory activity, prenylated flavonols 181–183 were isolated and characterized [66]. 8-(1,1-dimethylallyl)-5'-[(3-methylbut-2-enyl)-3',4',5,7-tetrahydroxyflavonol (181), papyriflavonol (182) and broussoflavonol (183) were observed to inhibit human erythrocyte AChE with IC50 values of 0.82, 3.1 and 2.7 M, respectively. Compound 181, the most potent, acted as a time-dependent, slow reversible inhibitor.

Isoorientin (184) and isovitexin (185) were identified as the compounds responsible for the AChE inhibition observed in the extracts from flowers and rhizomes of Iris pseudopomila (Iridaceae) from Italy [67]. Compound 184
was observed to be the highest inhibitor with an IC$_{50}$ = 26.8 µM while 185, lacking the 3’-hydroxy group in ring B, was observed to show an IC$_{50}$ value of 36.4 µM. Both compounds were also found to have the ability of significantly inhibiting BChE.

On the other hand, a pterocarpan with moderate AChE inhibition was isolated from the polar extract of *Zygophyllum eurypterum* (Zygophyllaceae) collected in Pakistan. Atricarpan D [(-)-2,9-dimethoxy-4-(5-oxohexyl)pterocarpan] (186) was observed to inhibit AChE with an IC$_{50}$ = 20.5 µM [68]. Interestingly, three other pterocarpans with similar structure were obtained along with atricarpan D but they were found to be inactive against AChE. Nevertheless, the four pterocarpans were all found to be BChE inhibitors.
A study conducted on AChE and BChE inhibitory activity of coumarins and naphtoquinones obtained from Mansonia gagei (Sterculiaceae) proposed a novel class of cholinesterase inhibitor, mansonones or 1,2-naphtoquinones [69]. The level of cholinesterase inhibition observed in this study seemed to correlate to the presence of a fused pyran ring and a substituent at C-6 being present in the molecule. Mansonone E (187) was observed to be the most active AChE (IC50 = 23.5 μM) and BChE inhibitor.

In several studies published during the period covered in the present review various phenolic compounds with different structural characteristics were reported as AChEi. Some of them are structurally simple such as gallic acid (188, IC50 = 5.85 μM) and ellagic acid (189, IC50 = 45.63 μM) [70]. Hopeahainol A (190), which was identified as a new compound isolated from Hopea hainensis, was observed to elicit a notable AChE inhibition (IC50 = 4.33 μM) with respect to huperzine A (IC50 = 1.6 μM), as a reversible mixed-type inhibitor [71].

The bioassay-guided fractionation of the extract from Terminalia chebula (Combretaceae) fruits allowed the isolation of 1,2,3,4,6-penta-O-galloyl-β-D-glucose (191) which demonstrated to be a significant AChE inhibitor (IC50 = 29.9 μM) [72]. This gallotanin which has been also isolated from other different sources and which is known by its diverse biological activities, was observed to exert good BChE inhibition and potent antioxidant activity (FRAP assay) in this study.

The bioassay-guided extraction of the stem bark of Knema laurina (Myristicaceae) yielded two active fractions (dichloromethane and hexane) which were subjected to chromatographic separation. That latter yielded five alkenyl phenol and salicylic acid derivatives 192 - 196, of which 192 and 193 were new compounds [73]. Compounds 192, 195 and 196, all having salicylic acid moiety, were observed to strongly inhibit AChE with an IC50 = 3.182, 2.172 and 0.573 μM, respectively. Compounds 193 and 194, with no carboxyl moiety, were observed to be good AChE inhibitors (IC50 = 17.224 and 13.114 μM, respectively). These findings suggest that the acidic group is key to good AChE inhibition. It was also observed that anti-AChE activity dramatically decreased when the acidic and the phenolic hydroxy group were methylated. Two catechol alkenyls were isolated from the fruits of Semecarpus anacardium (Anacardiaceae), a species used in Ayurvedic medicine for retarding and treatment of memory loss [74]. Compounds 197 and 198 were identified as active components of the dichloromethane extract through a fractionation guided by the detection of AChE inhibition. Microplate assay revealed that these catechol alkenyls are moderate and weak selective AChEi. Compound 197, with a double bond in the aliphatic chain, was identified as a stronger inhibitor (IC50 = 39.7 μM) with respect to compound 198, with two double bonds in the aliphatic chain (IC50 = 108 μM).
On the other hand, four structurally diverse AChEi were isolated from the polar extract of *Nelumbo nucifera* (Nelumbonaceae) stamens [75]. Cycloartenol (199), *p*-hydroxybenzoic acid (200), vanilloidoside (201) and nuciferoside (202) were found to elicit good and noncompetitive inhibition against AChE with an IC$_{50}$ = 11.89, 20.07, 4.55 and 3.2 μM, respectively. In the same study, compounds 199, 200 and 202 were observed to exert moderate BChE inhibition and compounds 199 - 202 were found to show no inhibition against BACE1.

**PLANT EXTRACTS, FRACTIONS AND ESSENTIAL OILS WITH AChE INHIBITORY ACTIVITY**

Table 1 summarizes the studies published from 2006 to 2012 on plant extracts, fractions and essential oils that have been found to be good AChE inhibitors (IC$_{50}$ < 500 μg/mL). Those plants included in other recent reviews were omitted [76, 77]. Extracts and fractions under further phytochemical studies that led to the discovery of AChE inhibitors were also omitted. Whenever possible, reference is made to the
### Table 1. Plant Extracts, Fractions and Essential Oils with AChE Inhibitory Activity

| Family and Botanical Name       | Type of Extract (Solvent) | Plant’s Parts | AChE Inhibition (%) | IC<sub>50</sub>       | Refs. |
|---------------------------------|---------------------------|---------------|---------------------|-----------------------|-------|
| **Acanthaceae**                 |                           |               |                     |                       |       |
| Andrographis paniculata         | H2O:EtOH                  | Aerial        |                     | 222.41 µg/ml          | [78]  |
| **Amaranthaceae**               |                           |               |                     |                       |       |
| Salsola oppositifolia           | Alkaloids                 | Aerial        |                     | 70.0 µg/ml            | [79]  |
| Salsola soda                    | Alkaloids                 | Aerial        |                     | 64.1 µg/ml            | [79]  |
| Salsola tragus                  | Alkaloids                 | Aerial        |                     | 30.2 µg/ml            | [79]  |
| **Amaryllidaceae**              |                           |               |                     |                       |       |
| Crinum jagus                    | MeOH                      | Leaf          | 74.25 (42 µg/ml)    |                       | [80]  |
| Crinum moorei                   | 50% MeOH                  | Bulb          |                     | 21.5 µg/ml            | [81]  |
|                                | PE                        |               | 18.9 µg/ml          |                       |       |
|                                | DCM                       |               | 2.9 µg/ml           |                       |       |
|                                | EtOH                      |               | 22.5 µg/ml          |                       |       |
| Nerine undulata                 | Alkaloids                 | Bulb          |                     | 14.3 µg/ml<sup>a</sup> | [82]  |
| Scadoxus multiflorus            | Alkaloids                 | Bulb          |                     | 313.5 µg/ml<sup>a</sup> | [82]  |
| Sprekelia formosissima          | Alkaloids                 | Bulb          |                     | 209.7 µg/ml<sup>a</sup> | [82]  |
| Zephyranthes grandiflora        | Alkaloids                 | Bulb          |                     | 39.2 µg/ml<sup>a</sup> | [83]  |
| **Anacardiaceae**               |                           |               |                     |                       |       |
| Harpephyllum caffrum            | DCM                       | Leaf          |                     | 0.17 mg/ml            | [84]  |
|                                | MeOH                      | Stem bark     |                     | 0.02 mg/ml            |       |
|                                |                           | Leaf          |                     | 0.12 mg/ml            |       |
| Pistacia atlantica             | H2O                       | Leaf          |                     | 0.87 µg/ml            | [85]  |
| Pistacia lentiscos              | H2O                       | Leaf          |                     | 13.67 µg/ml           | [85]  |
| Sclerocarya birrea              | DCM                       | Young stem    |                     | 0.15 mg/ml            | [84]  |
|                                | MeOH                      | Leaf          |                     | 0.10 mg/ml            |       |
|                                |                           | Operculum     |                     | 0.35 mg/ml            |       |
|                                |                           | Young stem    |                     | 0.47 mg/ml            |       |
| Spondias mombin                 | MeOH                      | Root bark     | 64.77 (42 µg/ml)    |                       | [80]  |
| **Apiceae**                     |                           |               |                     |                       |       |
| Centella asiatica               | H2O:EtOH                  | Whole plant   |                     | 106.55 µg/ml          | [78]  |
| **Apocynaceae**                 |                           |               |                     |                       |       |
| Geissospermum vellosii          | Alkaloids                 | Stem bark     |                     | 2.9 µg/ml             | [86]  |
| **Arecaceae**                   |                           |               |                     |                       |       |
| Colocasia antiquorum            | 50% MeOH                  | Tuber         |                     | 7.9 µg/ml             | [81]  |
|                                | PE                        |               | 6.4 µg/ml           |                       |       |
|                                | DCM                       |               | 168.1 µg/ml         |                       |       |
| Pinellia ternata                | Alkaloids                 | Tuber         |                     | 56.2 µg/ml            | [87]  |
| **Arecaceae**                   |                           |               |                     |                       |       |
| Phoenix dactylifera             | Hexane                    | Seed          |                     | 52.96 (300 µg/ml)     | [88]  |
| Family and Botanical Name          | Type of Extract (Solvent) | Plant’s Parts | AChE Inhibition (%) | IC$_{50}$ (Solvent) | Refs. |
|-----------------------------------|---------------------------|---------------|---------------------|----------------------|-------|
| **Asparagaceae**                  |                           |               |                     |                      |       |
| Leopoldia comosa                  | Hexane                    | Bulb          | 104.9 µg/ml         |                      | [89]  |
| **Asphodelaceae**                 |                           |               |                     |                      |       |
| Aloe ferox                        | 50% MeOH, PE, DCM         | Leaf          |                      | 84.0 µg/ml, 37.7 µg/ml, 62.6 µg/ml | [81]  |
| **Asteraceae**                    |                           |               |                     |                      |       |
| Achyrocline tomentosa             | Organic                   | Aerial        | 0.4847 mg/ml         |                      | [90]  |
| Arnica chamissonis ssp. foliosa  | MeOH, Hexane              | Flower        | 43 µg/ml, 29 µg/ml   |                      | [91]  |
| Chromolaena tequendamensis       | MeOH                      | Whole plant   | 359.36 mg/ml         |                      | [92]  |
| Eupatorium viscidum               | Organic                   | Aerial        | 0.4792 mg/ml         |                      | [90]  |
| Pulicaria stephanocarpa           | CHCl$_3$                  | Leaf          | 61.43 (0.2 mg/ml)    |                      | [93]  |
| Schistocarpa siniflori            | MeOH                      | Whole plant   | 145.31 mg/l          |                      | [92]  |
| Trichocline reptans               | Organic                   | Aerial        | 0.1118 mg/ml         |                      | [90]  |
| **Berberidaceae**                 |                           |               |                     |                      |       |
| Berberis darwinii                 | MeOH                      | Stem bark     | 1.23 µg/ml           |                      | [94]  |
| **Boraginaceae**                  |                           |               |                     |                      |       |
| Onosma bracteata                  | MeOH                      | Leaf          | 59.73 (250 µg/ml)    |                      | [95]  |
| **Buddlejaceae**                  |                           |               |                     |                      |       |
| Buddleja salvifolia               | DCM:MeOH (1:1)            | Whole plant   | 0.05 mg/ml           |                      | [96]  |
| **Bursaceae**                     |                           |               |                     |                      |       |
| Boswellia socotranao             | CHCl$_3$                  | Resin         | 71.21 (0.2 mg/ml)    |                      | [93]  |
| **Cistaceae**                     |                           |               |                     |                      |       |
| Cistus laurifolius                | EtOH                      | Leaf          | 80.07 (200 µg/ml)    |                      | [97]  |
| **Combretaceae**                  |                           |               |                     |                      |       |
| Terminalia bellirica              | MeOH                      | Fruit         | 14.37 µg/ml          |                      | [70]  |
| **Convolvulaceae**                |                           |               |                     |                      |       |
| Evolvalus alsinoides              | H$_2$O:EtOH               | Whole plant   | 141.76 µg/ml         |                      | [78]  |
| Ipomoea asarifolia                | MeOH                      | Leaf          | 0.12 µg/ml           |                      | [98]  |
| **Crassulaceae**                  |                           |               |                     |                      |       |
| Kalanchoe brasiliensis            | EtOAc                     | Leaf          | 0.16 mg/ml           |                      | [98]  |
| **Cucurbitaceae**                 |                           |               |                     |                      |       |
| Euretandra halbumii               | MeOH                      | Tuber         | 58.61 (0.2 mg/ml)    |                      | [93]  |
| **Cupressaceae**                  |                           |               |                     |                      |       |
| Juniperus phoenicea               | EtOH                      | Leaf          | 53.44 (400 µg/ml)    |                      | [99]  |
| Juniperus turbinata               | Phenolic                  | Leaf          | 83.84 (400 µg/ml)    |                      | [99]  |
Table 1. contd....

| Family and Botanical Name           | Type of Extract (Solvent) | Plant’s Parts | AChE Inhibition (%) | IC<sub>50</sub> | Refs. |
|-------------------------------------|---------------------------|---------------|---------------------|----------------|-------|
| **Ericaceae**                       |                           |               |                     |                |       |
| Rhododendron yedoense var. poukhanense | 80% MeOH                  | Bark          |                     | 169.01 µg/ml   | [100] |
| **Eucommiaceae**                   |                           |               |                     |                |       |
| Eucommia ulmoides                  | H<sub>2</sub>O            | Bark          |                     | 172 µg/ml      | [101] |
| **Euphorbiaceae**                  |                           |               |                     |                |       |
| Alchornia laxiflora                | MeOH                      | Stem bark     | 41.12 (42 µg/ml)    |                | [80]  |
| Cephalocroton socotranus           | CHCl<sub>3</sub>           | Bark          | 51.1 (0.2 mg/ml)    |                | [93]  |
| Jatropha curcas                    | MeOH                      | Leaf          | 0.25 mg/ml          |                | [98]  |
| Jatropha gossypiifolia             | MeOH                      | Leaf          | 0.05 mg/ml          |                | [98]  |
| **Fabaceae**                       |                           |               |                     |                |       |
| Acacia nilotica                    | H<sub>2</sub>O            | Root          | 0.079 mg/ml<sup>b</sup> |                | [102] |
| Acacia raddiana                    | H<sub>2</sub>O            | Bark          | 33.91 µg/ml         |                | [85]  |
| Cassia obtusifolia                | EtOH                      | Seed          | 81.6 µg/ml<sup>c</sup> |                | [103] |
| Chamaecrista mimosoides           | DCM:MeOH (1:1)            | Root          | 0.03 mg/ml          | 0.35 mg/ml     | [96]  |
| Genista tenera                     | EtOAc                     | Aerial        | 77.0 (70 µg/ml)     |                | [105] |
| Peltophorum pterocarpum            | MeOH                      | Leaf          | 49.5 (42 µg/ml)     | 68.85 (42 µg/ml) | [80]  |
| Schotia brachypepala               | DCM:MeOH (1:1)            | Bark          | 0.27 mg/ml          | 0.49 mg/ml     | [96]  |
| Senna alata                        | EtOAc                     | Leaf          | 0.08 mg/ml          |                | [98]  |
| Spatholobus suberectus             | H<sub>2</sub>O            | Whole plant   | 85 µg/ml            | 9 µg/ml        | [104] |
| Trigonella foenum-graecum          | EtOAc                     | Seed          | 53.00 µg/ml         | 9.23 µg/ml     | [106] |
| **Gobulariaceae**                  |                           |               |                     |                |       |
| Globularia alypum                  | H<sub>2</sub>O            | Root          | 16.67 µg/ml         |                | [85]  |
| **Guttiferaceae**                  |                           |               |                     |                |       |
| Calliphylhum inophyllurn           | MeOH                      | Root bark     | 56.52 (42 µg/ml)    |                | [80]  |
| **Hypericaceae**                   |                           |               |                     |                |       |
| Hypericum perforatum               | MeOH                      | Whole plant   | 178 µg/ml           |                | [91]  |
| **Illiciaceae**                    |                           |               |                     |                |       |
| Illicium verum                     | H<sub>2</sub>O:EtOH       | Fruit         | 58.67 µg/ml         | 44.94 µg/ml    | [107] |
|                                  | Butanol                    |               | 83.75 µg/ml         | 103.03 µg/ml   |       |
|                                  | EtOAc                      |               | 39.89 µg/ml         |                |       |
|                                  | CHCl<sub>3</sub>           |               |                     |                |       |
|                                  | Oil                        |               |                     |                |       |
| Family and Botanical Name | Type of Extract (Solvent) | Plant’s Parts | AChE Inhibition (%) | IC<sub>50</sub> | Refs. |
|--------------------------|---------------------------|---------------|---------------------|-----------------|-------|
| **Lamiaceae**            |                           |               |                     |                 |       |
| Cyclotrichium niveum     | EtOAc, DCM                | Whole plant   | 83.11 (250 µg/ml)   | 70.82 (250 µg/ml) | [108] |
| Hyssopus officinalis     | Hexane                    | Whole plant   | 55.0 (400 µg/ml)    |                 | [91]  |
| Lavandula viridis       | MeOH                      | Aerial        | 244.55 µg/ml        |                 | [109] |
| Marrubium vulgare       | Acetone                   | Aerial        | 62.70 (25 µg/ml)    |                 | [110] |
| Origanum ehrenbergii    | Essential oil             | Aerial        | 0.3 µg/ml           |                 | [111] |
| Origanum majorana       | Essential oil             | Leaf          | 36.40 µg/ml         |                 | [112] |
| Origanum syriacum       | Essential oil             | Aerial        | 1.7 µg/ml           |                 | [111] |
| Pycnostachys reticulata | 50% MeOH, EtOH            | Leaf          | 28.8 µg/ml          | 8.8 µg/ml       | [81]  |
| Salvia chionantha       | Essential oil             | Aerial        | 56.7 (500 µg/ml)    |                 | [113] |
| Salvia fruticosa        | DCM                       | Whole plant   | 51.07 (100 µg/ml)   |                 | [114] |
| Salvia leriisofolia     | Essential oil             | Aerial        | 0.32 µl/ml          |                 | [115] |
| Salvia miltiorrhiza     | H<sub>2</sub>O, EtOH      | Root          | 50 µg/ml            | 5 µg/ml         | [104] |
| Teucrium royleanum      | MeOH                      | Whole plant   | 52.4 (40 µg/0.2ml)  |                 | [116] |
| **Menispermaceae**      |                           |               |                     |                 |       |
| Stephania pierrei       | EtOH                      | Tuber         | 5.68 µg/ml          |                 | [117] |
| Tinospora cordifolia    | MeOH                      | Stem          | 38.36 µg/ml         |                 | [118] |
| **Moraceae**            |                           |               |                     |                 |       |
| Dorstenia gigas         | CHCl<sub>3</sub>          | Leaf          | 65.12 (0.2 mg/ml)   |                 | [93]  |
| Ficus religiosa         | MeOH                      | Stem bark     | 73.69 µg/ml         |                 | [118] |
| **Myristicaceae**       |                           |               |                     |                 |       |
| Myristica fragrans      | H<sub>2</sub>O:EtOH       | Seed          | 133.28 µg/ml        |                 | [78]  |
| Embelia ribes           | MeOH                      | Root          | 23.04 µg/ml         |                 | [118] |
| **Orchidaceae**         |                           |               |                     |                 |       |
| Orchis mascula          | MeOH                      | Root          | 56.99 (250 µg/ml)   |                 | [119] |
| **Paeoniaceae**         |                           |               |                     |                 |       |
| Paeonia lactiflora      | H<sub>2</sub>O, EtOH      | Root          | 20 µg/ml, 8 µg/ml   |                 | [104] |
| Paeonia veitchii        | H<sub>2</sub>O, EtOH      | Root          | 14 µg/ml, 45 µg/ml  |                 | [104] |
| **Papaveraceae**        |                           |               |                     |                 |       |
| Corydalis intermedia    | MeOH                      | Whole plant   | 84 (100 µg/ml)      |                 | [120] |
|                         | H<sub>2</sub>O            | Tuber         | 97 (100 µg/ml)      |                 |       |
|                         |                          | Whole plant   | 57 (100 µg/ml)      |                 |       |
|                         |                          | Tuber         | 78 (100 µg/ml)      |                 |       |
| Family and Botanical Name | Type of Extract (Solvent) | Plant’s Parts | AChE Inhibition (%) | IC₅₀ | Refs. |
|---------------------------|---------------------------|---------------|---------------------|------|-------|
| **Papaveraceae**          |                           |               |                     |      |       |
| Corydalis solida ssp. laxa| MeOH H₂O                  | Whole plant   | 89 (100 µg/ml)      |      | [120] |
|                           |                           | Tuber         | 96 (100 µg/ml)      |      |       |
|                           |                           | Whole plant   | 78 (100 µg/ml)      |      |       |
|                           |                           | Tuber         | 85 (100 µg/ml)      |      |       |
| Corydalis solida ssp. slivenensis | MeOH H₂O | Whole plant   | 82 (100 µg/ml)      |      | [120] |
|                           |                           | Tuber         | 97 (100 µg/ml)      |      |       |
|                           |                           | Whole plant   | 48 (100 µg/ml)      |      |       |
|                           |                           | Tuber         | 87 (100 µg/ml)      |      |       |
| **Phyllantaceae**         |                           |               |                     |      |       |
| Emblica officinalis       | MeOH                      | Fruit         | 29.26 µg/ml         |      | [70]  |
| **Pinaceae**              |                           |               |                     |      |       |
| Pinus halepensis          | EtOH Essential oil        | Needle        | 60.15 (200 µg/ml)   |      | [121] |
|                           |                           | Twig          | 83.91 (200 µg/ml)   |      |       |
| Pinus heldreichii subsp. leucodermis | Essential oil | Needle | 51.1 µg/ml | | [122] |
| Pinus nigra subsp. nigra  | Essential oil             | Needle        | 94.4 µg/ml          |      | [122] |
| Pinus nigra subsp. calabrica | Essential oil            | Needle        | 101.5 µg/ml         |      | [122] |
| Pinus pinaster            | Pycnogenol                | Bark          | 63.33 (200 µg/ml)   |      | [121] |
| **Piperaceae**            |                           |               |                     |      |       |
| Piper nigrum              | EtOH                      | Fruit         | 30.67 µg/ml         |      | [117] |
| **Poaceae**               |                           |               |                     |      |       |
| Cymbopogon jawarancusa    | MeOH                      | Whole plant   | 72.36 (250 µg/ml)   |      | [95]  |
| Cymbopogon schoenanthus   | Essential oil             | Fresh leaf (mountain reg./ desert reg.) | 0.26 / 0.67 mg/ml |      | [123] |
|                           |                           | Dried leaf (mountain reg./ desert reg.) | 0.44 / 0.52 mg/ml |      |       |
|                           |                           | Dried root (mountain reg./ desert reg.) | 0.27 / 0.32 mg/ml |      |       |
| Cymbopogon schoenanthus   | Hexane DCM EtOAc MeOH H₂O | Shoot (mountain reg./ desert reg.) | 0.50 / 0.54 mg/ml |      | [124] |
|                           |                           |               | 0.57 / 0.30 mg/ml   |      |       |
|                           |                           |               | 0.23 / 0.30 mg/ml   |      |       |
|                           |                           |               | 0.23 / 0.25 mg/ml   |      |       |
|                           |                           |               | 0.46 / 0.04 mg/ml   |      |       |
| **Polygonaceae**          |                           |               |                     |      |       |
| Fallopia multiflora       | H₂O EtOH                  | Root          | 13 µg/ml 65 µg/ml   |      | [104] |
| Rheum palmatum            | H₂O EtOH                  | Root and Rizhome | 32 µg/ml 18 µg/ml | | [104] |
| Ruprechtia apetala        | EtOH                      | Aerial        | 0.0779 mg/ml        |      | [90]  |
| **Portulacaceae**         |                           |               |                     |      |       |
| Portulaca oleracea        | Alkaloids                 | Upper part    | 29.4 µg/ml          |      | [87]  |
Table 1. contd….

| Family and Botanical Name | Type of Extract (Solvent) | Plant’s Parts | AChE Inhibition (%) | IC₅₀ | Refs. |
|---------------------------|---------------------------|---------------|---------------------|-----|------|
| **Rhamnaceae**            |                           |               |                     |     |      |
| *Rhamnus prinoides*       | H₂O                       | Root          | 0.201 mg/ml b       |     | [102]|
| **Rosaceae**              |                           |               |                     |     |      |
| *Leucosidea sericea*      | PE                        | Leaf          | 0.16 mg/ml          |     | [125]|
|                           | DCM                       | Stem          | 0.14 mg/ml          |     |      |
|                           | MeOH                      |               | 0.24 mg/ml          |     |      |
|                           | PE                        |               | 0.26 mg/ml          |     |      |
| **Rubiaceae**             |                           |               |                     |     |      |
| *Galium odoratum*         | Hexane                    | Whole plant   | 53.1 (400 µg/ml)    |     | [91] |
| *Morinda citrifolia*      | EtOH                      | Fruit         | 138.4 µg/ml         | 78.11 µg/ml | [126]|
|                           | CHCl₃                     |               |                     |     |      |
| *Morinda lucida*          | MeOH                      | Leaf          | 40.15 (42 µg/ml)    |     | [80] |
| **Rutaceae**              |                           |               |                     |     |      |
| *Citrus aurantifolia*     | Essential oil             | Leaf          | 139 µg/ml           |     | [127]|
| *Citrus medica*           | Essential oil             | Peel          | 171.3 µg/ml         |     | [128]|
| *Ruta graveolens*         | MeOH                      | Whole plant   | 59.1 (100 µg/ml)    |     | [91] |
|                           | Hexane                    |               | 34 µg/ml            |     |      |
| *Zanthoxylum coco*        | Organic                   | Aerial        | 0.1579 mg/ml        |     | [90] |
| **Solanaceae**            |                           |               |                     |     |      |
| *Solanum leucocarpum*     | MeOH                      | Whole plant   | 204.59 mg/l         |     | [92] |
| *Withania somnifera*      | MeOH                      | Root          | 33.38 µg/ml         |     | [118]|
| *Witheringia coccoboides* | MeOH                      | Whole plant   | 220.68 mg/l         |     | [92] |
| **Valerianaceae**         |                           |               |                     |     |      |
| *Nardostachys jatamansi*  | H₂O:EtOH                  | Rhizome       | 130.11 µg/ml        | 47.21 µg/ml | [78] |
|                           | MeOH                      |               |                     |     | [118]|
| **Zingiberaceae**         |                           |               |                     |     |      |
| *Kaempfera parviflora*    | EtOH                      | Rhizome       | 20.64 µg/ml         |     | [117]|

DCM: dichloromethane; MeOH: methanol; EtOH: ethanol; PE: petroleum ether; EtOAc: ethyl acetate

bHuman blood AChE.

cBovine erythrocyte AChE.

dMouse brain homogenized.

part of the plant used in each study reported. AChE inhibitory activity is reported in the same way as it was reported by authors and IC₅₀ values were chosen instead of inhibition percentages when both were available.

**CONFLICT OF INTEREST**

The author(s) confirm that this article content has no conflict of interest.

**ACKNOWLEDGEMENTS**

CONICET, CIC, UNS and ANPCYT.

**REFERENCES**

[1] Chopra, K.; Misra, S.; Kuhad, A. Current perspectives on pharmacotherapy of Alzheimer’s. *Expert. Opin. Pharmacother.*, 2011, 12, 335-350.

[2] Ellman, G.L.; Courtney, K.D.; Andres, V.; Featherstone, R.M. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem. Pharmacol.*, 1961, 7, 88-95.

[3] Lopez, S.; Bastida, J.; Viladomat, F.; Codina, C. Acetylcholinesterase inhibitory activity of some Amaryllidaceae alkaloids and *Narcissus* extracts. *Life Sci.*, 2002, 71, 2521-2529.

[4] Rhee, I.K.; van de Meent, M.; Ingkaninan, K.; Verpoorte, R. Screening for acetylcholinesterase inhibitors from Amaryllidaceae
using silica gel thin-layer chromatography in combination with bioactivity staining. *J. Chromatogr. A*, 2001, 915, 217-223.

[5] Marston, A.; Kissling, J.; Hostettmann, K. A rapid TLC bioaegographic method for the detection of acetylcholinesterase and butyrylcholinesterase inhibitors in plants. *Phytochem. Anal.*, 2002, 13, 51-54.

[6] Di Giovanni, S.; Borloz, A.; Urbain, A.; Marston, A.; Hostettmann, K.; Carrupt, P.A.; Reist, M. In vitro screening assays to identify natural or synthetic acetylcholinesterase inhibitors: thin layer chromatography versus microplate methods. *Eur. J. Pharm. Sci.*, 2008, 33, 109-119.

[7] Houghton, P.J.; Ren, Y.; Howes, M.J. Acetylcholinesterase inhibitors from plants and fungi. *Nat. Prod. Rep.*, 2006, 23, 181-199.

[8] Williams, P.; Sorribas, A.; Howes, M.J. Natural Products as a source of Alzheimer’s drugs leads. *Nat. Prod. Rep.*, 2011, 28, 48-77.

[9] Mukherjee, P.K.; Kumar, V.; Mal, M.; Houghton, P.J. Acetylcholinesterase inhibitors from plants. *Phytochemistry*, 2007, 68, 289-300.

[10] Orhan, G.; Orhan, I.; Subutay-Oztekin, N., Ak, F.; Sener, B. Contemporary anticholinesterase pharmaceuticals of natural origin and their synthetic analogues for the treatment of Alzheimer’s disease. *Recent. Pat. CNS Drug Discov.*, 2009, 4, 43-51.

[11] Rahman, A.U.; Idrees, A.; Chatha, N.; Ghauri, M.N.; Mesiak, M.A.; Khan, M.R.; Gilani, A.H.; Choudhary, M.I. New natural cholinesterase inhibiting and calcium channel blocking quinoline alkaloids. *J. Enzyme Inhib. Med. Chem.*, 2006, 21, 703-710.

[12] Cardoso-Lopes, E.M.; Maier,J.A.; da Silva, M.R.; Regasini, L.O.; Simote, S.Y.; Lopes, N.P.; Pirani, J.R.; da Silva Bolzani, V.; Marx Young, M.C. Alkaloids from stems of *Esenbeckia leucopus* Engl. (*Rutaceae*) as potential treatment for Alzheimer Disease. *Molecules*, 2010, 15, 9205-9213.

[13] Yang, Z.; Zhang, D.; Ren, J.; Yang, M. Skimmianine, a potent acetylcholinesterase inhibitor. *J. Enzyme Inhib. Med. Chem.*, 2010, 25, 847-852.

[14] Yang, Z.; Duan, D.Z.; Du, J.; Yang, M.J.; Li, S.; Yao, X.J. Geranoside methyl ether, a corynanthe-type indole alkaloid from *Uncaria rhynchophylla* as a potential acetylcholinesterase inhibitor. *Nat. Prod. Res.*, 2012, 26, 22-28.

[15] Seidl, C.; Correia, B.L.; Stinghen, A.E.; Santos, C.A. Acetylcholinesterase inhibitory activity of uleine from *Himantandra lancifolius*. *Z. Naturforsch.* C, 2010, 65, 440-444.

[16] Seidl, C.; Correia, B.L.; Stinghen, A.E.; Santos, C.A. Acetylcholinesterase inhibitory activity of uleine from *Himantandra lancifolius*. *Z. Naturforsch.* C, 2010, 65, 440-444.

[17] Seidl, C.; Correia, B.L.; Stinghen, A.E.; Santos, C.A. Acetylcholinesterase inhibitory activity of uleine from *Himantandra lancifolius*. *Z. Naturforsch.* C, 2010, 65, 440-444.

[18] Seidl, C.; Correia, B.L.; Stinghen, A.E.; Santos, C.A. Acetylcholinesterase inhibitory activity of uleine from *Himantandra lancifolius*. *Z. Naturforsch.* C, 2010, 65, 440-444.

[19] Seidl, C.; Correia, B.L.; Stinghen, A.E.; Santos, C.A. Acetylcholinesterase inhibitory activity of uleine from *Himantandra lancifolius*. *Z. Naturforsch.* C, 2010, 65, 440-444.
steroidal alkaloids from Sarcococca saligna and their cholinesterase inhibitory activity. Steroids, 2004, 69, 735-741.

Devkota, K.P.; Lenta, B.N.; Choudhary, M.I.; Naz, Q.; Fekam, F.B.; Rosenthal, P.J.; Sewald, N. Cholinesterase inhibiting and antiplasmodial steroidal alkaloids from Sarcococca hookeriana. Chem. Pharm. Bull. (Tokyo), 2007, 55, 1397-1401.

Devkota, K.P.; Lenta, B.N.; Wansi, J.; Choudhary, M.I.; Kisanga, D.P.; Naz, Q.; Samreen; Sewald, N. Bioactive 5α-Pregnanetype steroidal alkaloids from Sarcococca hookeriana. J. Nat. Prod., 2008, 71, 1481-1484.

Ata, A. In Studies in Natural Products Chemistry, 1st Edition, Vol. 38, Rahman, A.U., Ed.; Elsevier B.V.: Amsterdam, 2012, pp. 225-245.

Ata, A.; Iverson, C.D.; Kalhari, K.S.; Akhter, S.; Betteridge, J.; Meshkatalasadat, M.H.; Orhan, I.; Sener, B. Tripterpenoidal alkaloids from Basus hyrcana and their enzyme inhibitory, anti-fungal and anti-leishmanial activities. Phytochemistry, 2010, 71, 1780-1786.

Matotcho, W.L.; James, A.; Lam, C.W.; Kozer, D.A.; Ata, A.; Gengan, R. Tripterpenoidal alkaloids from Basus natalensis and their acetylcholinesterase inhibitory activity. J. Nat. Prod., 2010, 73, 1858-1862.

Rahman, A.U.; Akhtar, M.N.; Choudhary, M.I.; Tsuda, Y.; Sener, B.; Khalid, A.; Parvez, M. New steroidal alkaloids from Fritillaria imperialis and their cholinesterase inhibiting activities. Chem. Pharm. Bull. (Tokyo), 2002, 50, 1013-1016.

Lin, B.Q.; Ji, H.; Li, P.; Fang, W.; Jiang, Y. Inhibitors of acetylcholine esterase in vitro - Screening of steroidal alkaloids from Fritillaria species. Planta Med., 2006, 72, 814-818.

Yang, Z.; Duan, D.Z.; Xue, W.W.; Yao, X.J.; Li, S. Steroidal alkaloids from Holarrhena antidysenterica as acetylcholinesterase inhibitors and the investigation for structure-activity relationships. Life Sci., 2012, 90, 929-933.

Eldeen, I.M.; Van Heerden, F.R.; Van Staden, J. In vitro biological activities of niloticane, a new bioactive cassane diterpene from the bark of Acacia nilotica subsp. kraussiana. J. Ethnopharmacol., 2010, 128, 555-560.

Hung, T.M.; Luan, T.C.; Vinh, B.T.; Cuong, T.D.; Min, B.S. Labdanetype diterpenoids from Leonurus heterophyllus and their cholinesterase inhibitory activity. Phytother. Res., 2011, 25, 611-614.

Khan, I.; Nisar, M.; Khan, N.; Saeed, M.; Naheed, S.; Fazal-ur-Rehman, Ali; F.; Karim; N.; Kaleam, W.A.; Qayum, M.; Ahmad, H.; Khan, I.A. Structural insights to investigate Conypodiol as a cholinesterase-inhibition studies of sterols from Emblica officinalis. J. Ethnopharmacol., 2009, 1255-1261.

Riaz, N.; Nawaz, S.A.; Mukhtar, N.; Malik, A.; Afza, N.; Ali, S.; Ullah, S.; Muhammad, P.; Choudhary, M.I. Isoenzyme and enzyme-inhibition studies of the chemical constituents from Ajuga bracteosa. Chem. Biodivers., 2007, 4, 72-83.

Ahmed, E.; Nawaz, S.A.; Malik, A.; Choudhary, M.I. Isolation and cholinesterase-inhibition studies of sterols from Haloxylon recurvum. Bioorg. Med. Chem. Lett., 2006, 16, 573-580.

Awang, K.; Chan, G.; Litauon, M.; Ismail, N.H.; Martin, M.T.; Gueritte, F. 4-Phenylcoumarins from Mesua elegans with acetylcholinesterase inhibitory activity. Bioorg. Med. Chem., 2010, 18, 7873-7877.

Khan, M.T.; Orhan, I.; Senol, F.S.; Kartal, M.; Sener, B.; Dvorska, M.; Smekjel, K.; Slapotov, T. Cholinesterase inhibitory activities of some flavonoid derivatives and chosen xanthone and their molecular docking studies. Chem. Biol. Interact., 2009, 181, 383-389.

Urbain, A.; Marston, A.; Siatro Grilo, L.; Bravo, J.; Purevy, O.; Purevsuren, B.; Batsuen, D.; Reist, M.; Curtault, P.-A.; Hostettmann, K. Xanthones from Gentianella amarella ssp. acuta of some flavonoid derivatives and chosen xanthone and their molecular docking studies. J. Nat. Prod., 2008, 71, 895-897.

Cho, J.K.; Ryu, Y.B.; Curtis-Long, M.J.; Ryu, H.W.; Yue, H.J.; Kim, D.W.; Kim, H.J.; Lee, W.S.; Park, K.H. Cholinesterase inhibitory effects of geranylflavonoids from Paulownia tormentosa fruits. Bioorg. Med. Chem., 2012, 2059-2602.

Jung, H.A.; Jin, S.E.; Park, J.S.; Choi, J.S. Antidiabetic complications and anti-alzheimer activities of sophoralesvenol, a prenylated flavonol from Sophora flavescens, and its structure-activity relationship. Phyther. Res., 2011, 25, 709-715.
memory impairments induced by scopolamine or transient cerebral hypoperfusion in mice. J. Pharmacol. Sci., 2007, 105, 82-93.

[104] Lin, H.Q.; Ho, M.T.; Lai, L.S.; Wong, K.K.; Shaw, P.C.; Wan, D.C. Anti-acetylcholinesterase activities of traditional Chinese medicine for treating Alzheimer's disease. Chem. Biol. Interact., 2008, 175, 352-354.

[105] Rauter, A.P.; Martins, A.; Lopes, R.; Ferreira, J.; Serralheiro, L.M.; Araújo, M.E.; Borges, C.; Justino, J.; Silva, F.V.; Goulart, M.; Thomas-Oates, J.; Rodrigues, J.A.; Edwards, E.; Noronha, J.P.; Pinto, R.; Mota-Filipe, H. Bioactivity studies and chemical profile of the antidiabetic plant Genista tenera. J. Ethnopharmacol., 2009, 122, 384-393.

[106] Satheeshkumar, N.; Mukherjee, P.K.; Bharda, S.; Saha, B.P. Acetylcholinesterase enzyme inhibitory potential of standardized extract of Trigonella foenum graecum L and its constituents. Phytomedicine, 2010, 17, 292-295.

[107] Bharda, S.; Mukherjee, P.K.; Kumar, N.S.; Bandypadhyay, A. Anticholinesterase activity of standardized extract of Illicium verum Hook. f. fruits. Flotroparia, 2011, 82, 342-346.

[108] Orhan, I.; Senol, F.S.; Gülpinar, A.R.; Kartal, M.; Sekeroglu, N.; Senol, F.S.; Orhan I.; Celep F.; Kahraman, A.; Do, S.; Lin, H.Q.; Ho, M.T.; Lau, L.S.; Wong, K.K.; Shaw, P.C.; Wan, D.C. Anti-acetylcholinesterase activities of traditional Chinese medicine for treating Alzheimer’s disease. Chem. Biol. Interact., 2008, 175, 352-354.

[109] Tavares, L.; McDougall, G.J.; Fortalezas, S.; Stewart, D.; Ferreira, R.; Ashraf, M.; Ahmad, K.; Ahmad, I.; Ahmad, S.; Arshad, S.; Shah, M.; Bakthir, H.; Ali, N.A.A.; Arnold, N.; Teichert, A.; Wessjohann, L. The neuroprotective potential of phenolic-promising Brazilian medicinal plants. J. Med. Assoc. Thai., 2011, 94, 518-525.

[110] Costa, P.; Gonçalves, S.; Andrade, P.B.; Valentão, P.; Romano, M.; Orhan, I. Screening of selected Indian medicinal plants for acetylcholinesterase inhibitory activity. Ind. Crop. Prod., 2010, 32, 638-644.

[111] Altun, A.; Orhan, I.; Senol, F.S.; Gülpinar, A.R.; Hoşşal, S.; Kartal, M. Screening of selected plants for the treatment of Alzheimer's disease. J. Ethnopharmacol., 2010, 129, 384-393.

[112] Teichart, H.; Ali, N.A.A.; Arnold, N.; Tavares, L.; McDougall, G.J.; Fortalezas, S.; Stewart, D.; Ferrer, R.B.; Santos, C.N. Acetylcholinesterase and NADH oxidase inhibitory activity of some medicinal plants. Food Chem. Toxicol., 2011, 49, 2086-2089.

[113] Adsersen, A.; Gauguin, B.; Gudiksen, L.; Jäger, A.K. Screening of selected medicinal plants for acetylcholinesterase inhibitory activity. Acta Pharm., 2011, 60, 119-128.

[114] Costa, P.; Gonçalves, S.; Andrade, P.B.; Valentão, P.; Romano, M. Screening of selected Indian medicinal plants for acetylcholinesterase inhibitory activity. Acta Pharm., 2011, 60, 119-128.

[115] Nakano, J.; Horie, H.; Kato, H.; Nakashima, T.; Yamauchi, T.; Shimada, K.; Iwabuchi, N. Inhibitory effect of Lavandula viridis on Fe²⁺-induced lipid peroxidation, antioxidant and anti-cholinesterase properties. Food Chem., 2011, 126, 1779-1786.

[116] Orhan, I.E.; Belhattab, R.; Senol, F.S.; Gülpinar, A.R.; Hoşşal, S.; Kartal, M. Anticholinesterase activity of endemic plant extracts from Soqotra. J. Ethnopharmacol., 2009, 128, 638-644.

[117] Chen, J.H. The seed extract of Rhamnus prinoides D.C. Anti-acetylcholinesterase activities of traditional Chinese medicinal plants. J. Med. Assoc. Thai., 2011, 94, 518-525.

[118] Orhan, I.; Senol, F.S.; Gülpinar, A.R.; Kartal, M.; Sekeroglu, N.; Deveci, M.; Kan, Y.; Sener, B. Acetylcholinesterase inhibitory and antioxidant properties of Cyclochilum niveum, Thymus praecox subsp. causcasicus var. causcasicus, Echinacea purpurea and E. pallida. Food Chem. Toxicol., 2009, 47, 1304-1310.

[119] Orhan, I.; Senol, F.S.; Gülpinar, A.R.; Kartal, M.; Sekeroglu, N.; Deveci, M.; Kan, Y.; Sener, B. Inhibitory activity of Lavandula viridis on Fe²⁺-induced lipid peroxidation, antioxidant and anti-cholinesterase properties. Food Chem., 2011, 126, 1779-1786.

[120] Orhan, I.E.; Belhattab, R.; Senol, F.S.; Gulpinar, A.R.; Hosbas, S.; Kartal, M. Profiling of cholinesterase inhibitory and antioxidant activities of Artemisia abrotanum, A. herba-alba, A. fragnes, Marrubium vulgare, M. astracnum, Origanum vulgare subsp. glandulosum and essential oil analysis of two Artemisia species. Ind. Crop. Prod., 2010, 32, 566-571.

[121] Orhan, I.E.; Belhattab, R.; Senol, F.S.; Gulpinar, A.R.; Hosbas, S.; Kartal, M. Profiling of cholinesterase inhibitory and antioxidant activities of Artemisia abrotanum, A. herba-alba, A. fragnes, Marrubium vulgare, M. astracnum, Origanum vulgare subsp. glandulosum and essential oil analysis of two Artemisia species. Ind. Crop. Prod., 2010, 32, 566-571.

[122] Orhan, I.E.; Belhattab, R.; Senol, F.S.; Gülpinar, A.R.; Hoşşal, S.; Kartal, M. Anticholinesterase activity of endemic plant extracts from Soqotra. J. Ethnopharmacol., 2009, 128, 638-644.

[123] Tel, G.; Ortuz, M.; Duru, M.E.; Harmandar, M.; Topcu, G. Chemical composition of the essential oil and hexane extract of Salvia chionantha and their antioxidant and anticholinesterase activities. Food Chem. Toxicol., 2010, 48, 3189-3193.

[124] Orhan, I.E.; Belhattab, R.; Senol, F.S.; Gulpinar, A.R.; Hoşşal, S.; Kartal, M. Profiling of cholinesterase inhibitory and antioxidant activities of Artemisia abrotanum, A. herba-alba, A. fragnes, Marrubium vulgare, M. astracnum, Origanum vulgare subsp. glandulosum and essential oil analysis of two Artemisia species. Ind. Crop. Prod., 2010, 32, 566-571.

[125] Orhan, I.E.; Belhattab, R.; Senol, F.S.; Gülpinar, A.R.; Hoşşal, S.; Kartal, M. Profiling of cholinesterase inhibitory and antioxidant activities of Artemisia abrotanum, A. herba-alba, A. fragnes, Marrubium vulgare, M. astracnum, Origanum vulgare subsp. glandulosum and essential oil analysis of two Artemisia species. Ind. Crop. Prod., 2010, 32, 566-571.

[126] Ho, M.T.; Lau, L.S.; Wong, K.K.; Shaw, P.C.; Wan, D.C. Anti-acetylcholinesterase activities of traditional Chinese medicine for treating Alzheimer’s disease. Chem. Biol. Interact., 2008, 175, 352-354.

[127] Chen, J.H. The seed extract of Rhamnus prinoides D.C. Anti-acetylcholinesterase activities of traditional Chinese medicinal plants. J. Med. Assoc. Thai., 2011, 94, 518-525.

[128] Orhan, I.E.; Belhattab, R.; Senol, F.S.; Gulpinar, A.R.; Hoşşal, S.; Kartal, M. Anticholinesterase activity of endemic plant extracts from Soqotra. J. Ethnopharmacol., 2009, 128, 638-644.

[129] Tel, G.; Ortuz, M.; Duru, M.E.; Harmandar, M.; Topcu, G. Chemical composition of the essential oil and hexane extract of Salvia chionantha and their antioxidant and anticholinesterase activities. Food Chem. Toxicol., 2010, 48, 3189-3193.
for acetylcholinesterase inhibitory activity. J. Ethnopharmacol., 2006, 104, 418-422.

[121] Ustun, O.; Senol, F.; Kurkcuoglu, M.; Orhan, I.; Kartal, M.; Baser, K. Investigation on chemical composition, anticholinesterase and antioxidant activities of extracts and essential oils of Turkish Pinus species and pycnogenol. Ind. Crop. Prod., 2012, 38, 115-123.

[122] Bonesi, M.; Menichini, F.; Tundis, R.; Loizzo, M.R.; Conforti, F.; Passalacqua, N.G.; Statti, G.A.; Menichini, F. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of Pinus species essential oils and their constituents. J. Enzym. Inhib. Med. Ch., 2010, 25, 622-628.

[123] Khadri, A.; Serralheiro, M.L.M.; Nogueira, J.M.F.; Neffati, M.; Smiti, S.; Araújo, M.E.M. Antioxidant and antiacetylcholinesterase activities of essential oils from Cymbopogon schoenanthus L. Spreng. Determination of chemical composition by GC–mass spectrometry and 13C NMR. Food Chem., 2008, 109, 630-637.

[124] Khadri, A.; Neffati, M.; Smiti, S.; Falé, P.; Lino, A.R.L.; Serralheiro, A.M.; Araújo, M.E.M. Antioxidant, antiacetylcholinesterase and antimicrobial activities of Cymbopogon schoenanthus L. Spreng (lemon grass) from Tunisia. LWT-Food Sci. Technol., 2010, 43, 331-336.

[125] Aremu, A.O.; Amoo, S.O.; Ndhlala, A.R.; Finnie, J.F.; Stadenm J.V. Antioxidant activity, acetylcholinesterase inhibition, iridoid content and mutagenic evaluation of Leucosidea sericea. Food Chem. Toxicol., 2011, 49, 1122-1128.

[126] Pachauri, S.D.; Tota, S.; Khandelwal, K.; Verma, P.R.; Nath, C.; Hanif, K.; Shukla, R.; Saxena, J.K., Dwivedi, A.K. Protective effect of fruits of Morinda citrifolia L. on scopolamine induced memory impairment in mice: A behavioral, biochemical and cerebral blood flow study. J. Ethnopharmacol., 2012, 139, 34-41.

[127] Chaiyana, W.; Okonogi, S. Inhibition of cholinesterase by essential oil from food plant. Phytomedicine, 2012, 19, 836-839.

[128] Menichini, F.; Tundis, R.; Bonesi, M.; de Cindio, B.; Loizzo, M.R.; Conforti, F., Statti, G.A.; Menabeni, R.; Bettini, R.; Menichini, F. Chemical composition and bioactivity of Citrus medica L. cv. Diamante essential oil obtained by hydrodistillation, cold-pressing and supercritical carbon dioxide extraction. Nat. Prod. Res., 2011, 25, 789-799.