Natural products and their derived compounds inhibitors of the enzyme acetylcholinesterase

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Abstract
Alzheimer’s disease (AD) is a progressive, neurodegenerative pathology that primarily affects the elderly population, and is estimated to account for 50-60% of dementia cases in persons over 65 years of age. The main characteristics connected with AD implicate the dysfunction of cognitive role, mainly loss of memory. While, the main features linked with AD at later stages include deficits of language, depression and problems associated with behavior. One of the most important approaches for medication of this disease is to improve level of the acetylcholine in the brain tissues using inhibitors of acetylcholinesterase (AChE). The present work reviews the literature on natural products from plants and plant-derived compounds inhibitors of enzyme acetylcholinesterase.

Keywords: Alzheimer’s disease; Acetylcholinesterase inhibitors; Secondary metabolites; Plant extracts; essential oils

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Introduction
The enzyme acetylcholinesterase (AChE) catalysis the hydrolysis of the ester bound of acetylcholine (ACh) to terminate the impulse transmitted action of ACh through cholinergic synapses [1]. Although the primarily cause of Alzheimer’s disease (AD) is not clearly understood yet, AD is firmly linked with cholinergic transmission impairment. A number of AChE inhibitors have been considered for the symptomatic treatment of AD as the most useful relieving strategy [2]. Cholinesterase reversible inhibitors are newly testing clinically for medication of Alzheimer’s disease. The inhibitors of cholinesterase may react with the cholinergic system to ameliorate the deficits in memory as well as patients cognitive function by decreasing the acetylcholine breakdown at the site of synopsis in the brain. However, the therapeutic window is small, and testing of the inhibitory effect on acetylcholinesterase (AChE) in erythrocytes has been proposed as a guide to the efficacy and safety of putative therapies. Epidemiological data indicate a potentially considerable increase in the prevalence of the disease over the next two decades [3]. AD affects up to 5% of people over 65 years, rising to 20% of those over 80 years [1]. Most strategies of treatment have
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been essentially relies on the hypothesis of cholinergic system declared that impairments in patients memory with AD result from dysfunction of central cholinergic system in brain. Cholinergic neurotransmission is specially affected in patients with Alzheimer’s disease. One of the promising candidates approaches for medication of AD is to promote the level of brain acetylcholine using inhibitors of acetylcholinesterase [1]. Various inhibitors of AChE are being examined for the medication of AD. However, only tacrine, donepezil, rivastigmine and galantamine have been approved by the Food and Drug Administration in the United States [4]. Monoamine oxidase B (MAO-B) inhibitors is considered one among other approaches under examination, have also been suggested for AD treatment. Recently, the activity of MAO-B was found to be rise up to 3-fold in the different brain regions in patients with AD comparing with controls. This elevation in the activity of MAO-B causes an increase of hydroxyl radicals, which has been associated with the progress of plaques of Aβ. However, Aβ plaques is the primary senile plaques component and any compound capable of to inhibit plaques aggregation might be considered as promising candidate for AD medication [5]. Huge numbers of plants world wide have been involved in the remedies of traditional medicine. One of the natural compound is Huperzine A which is isolated from Huperzia serrata (Thumb.) as a potent AChE. inhibitor. In a previous paper this research group has reviewed crude plant acts and chemically defined molecules with potential antitumor activity for mammary (Barbosa-[1], for the treatment of Parkinson’s disease [6], with antileishmanial (Rocha et al., 2005) [7] and anti inflammatory activity [1]. The present work reviews the literature on natural product and natural product -derived compounds inhibitors of enzyme acetylcholinesterase.

Plant extracts inhibitors of acetylcholinesterase enzyme

Several reviews on the newly discovered AChEi obtained from plants, fungus and marine organisms [8]. Alkaloid group is considered as the majority of these AChEi. However, various non-alkaloidal and promising AChEi have been investigated from natural sources, such as terpenoids, flavonoids and other phenolic compounds. The inhibition of neurotransmitter; acetylcholine is occurred firstly by acetylcholinesterase (AChE) and secondly by butyryl cholinesterase (BChE), considered to have an important function in the AD pathology [8]. Despite AD unknown etiology, rise amount of acetylcholine through inhibition of AChE has been demonstrated as the most promising strategy for AD treatment. However, the present drugs (tacrine, rivastigmine and donepezil) with AChE inhibitory activity possess some side effects [8]. Consequently, it is compulsory to develop new drugs in order to combat AD [9]. Since AD, one of the most common cause of death worldwide, has become a threaten to public health, new treatment strategies based on medicinal plants have been focused [2]. A recent research with natural plants from Brazil declared promising output for the Amburana cearensis, Lippia sidoides, Paullinia cupana, Plathymiscium floribundum and Solanum as Peru species [10]. Since these species have been implicated in memory dysfunction medication in some folk medicines. Researchers are 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 [8].

ALKALOIDS WITH ache INHIBITORY ACTIVITY

The quinoline alkaloids 3-hydroxy-2,2,6-trimethyl 3,4,5,6-tetrahydro-2H-pyran [3,2-c] quinoline-5-one, ribalinine and methyl isoplatydesmine isolated from the aerial parts of
Skimmia laureola (Rutaceae) were found to be AChE inhibitors with $K_i = 110.0, 30.0$ and $30.0 \mu M$, respectively [11]. These alkaloids were also observed to evidence butyryl cholinesterase (BChE) inhibition. However, of the Esenbeckia leiocarpa (Rutaceae), alkaloids; leptomerine and kokusaginine showed no AChE inhibitory activity, was also reported [11]. These alkaloids were reported in another Rutaceae, Zanthoxylum nitidum, demonstrating a moderate activity of AChE inhibition [12]. Nelumbo nucifera is a well-known medicinal plant belonging to the Nelumbonaceae family which was studied due to its therapeutic potential[13]. Study on Corydalis (Papaveraceae) genus which are implicated in the medication of memory dysfunction reported the presence of benzylisoquinoline alkaloids with anti-AChE activity [14]. C. turgescens was reported to have AChE inhibitory activity due to the presence of is quinoline alkaloids stylopine, epiberberine, pseudodehydrocorydaline, pseudopeptide and pseudo berberine. [15]. Six protoberberine alkaloids were characteristics in Copris chinensis rhizomes are used for the medication of different disorders in Chinese folk medicine. Six protoberberine alkaloids were identified in rhizomes of Copris chinensis which are traditionally used in Chinese medicine for the treatment of various diseases. Also, rhizomes of coptidis and their active alkaloids were found to have cognitive-stimulating and neuroprotective function [16]. The anti-AChE activity of these alkaloids showed that the IC50 values of berberine, palmatine, jateorhizine, coryptisine and groenlandicine ranged between 0.44 and 0.80 $\mu M$ while that of epiberberine was slightly higher (IC50 = 1.07 $\mu M$) [16]. Groenlandicine and berberine were found to have BChE inhibitory activity and epiberberine was reported markedly inhibited betasecretase (BACE1) [16].

The alkaloids (+)-canadaline and (+)-canadine, from Corydalis cava were documented to have a moderate inhibitory activity of AChE [17]. On the other hand, Stephania venosa (Menispermeaceae), was reported to have AChE inhibitory activity. The ethanolic extract of S. venosa was subjected to bioassay-guided fractionation to identify AChEi [18]. A typical fractionation tools was applied to know the AChE inhibition compounds in Chelidonium majus (Papaveraceae) [19]. Fractionation from the stems of Ervatamia hainanensis (Apocynaceae), a plant used in traditional Chinese medicine, allowed the isolation of several monoterpene indole alkaloids, some of them showing a potent AChE inhibitory activity [20]. For example, coronaridine and voacangine, 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$\mu M$, respectively, these values being similar to that of galanthamine (3.2 $\mu M$). On the other hand, 10-hydroxy coronaridine was found to evidence a reduced AChE inhibition (IC50 = 29 $\mu M$), which was attributed to the introduction of a hydroxyl group to the aromatic ring. The indole alkaloids coronaridine and voacangine, both detected in the stalks of Tabernaemontana australis (Apocynaceae), had been formerly identified as AChEi but no inhibition values were reported [21]. The genus Tabernaemontana is known for the wide variety of unusual bioactive indole alkaloids it produces. The bisindole alkaloids isolated from T. divaricata roots are considered potent activity against AChE. The alkaloid crude extract of T. divaricata root was reported to produce four bisindole alkaloids [18]. The research of inhibitory activity of AChE of Himatanthus lancifolius (agoniada) led to the characterization and isolation of active extracts and in turn the isolation of an active indol alkaloid; uleine, [22]. 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[14]. In the study of new products of natural sources of galanthamine and other Amaryllidaceae alkaloids with anti-AChE activity, bulbs and leaves of Hippeastrum papilio were determined. Galanthamine, the
already known alkaloids narwedine, haemanthamine, 11-hydroxyvittatine, 8-O-demethylmaritidine and vittatine as well as the new alkaloid 11-beta-hydroxy galanthamine were all isolated and of all of them galanthamine was obtained in significant amounts [23]. 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 and lycorine N-oxide and seven known alkaloids namely, 1-acetyl-carboline, incartine, N-trans feruloyl tyramine, lycorine, O-methylnorbelladine, vittatine and 11-hydroxyvittatine [24]. The alkaloids effect as AChEi was identified, however, incartine N-oxide only was noticed to elicit a moderate inhibitory activity (IC50=34.50 µM), incartine was observed to be weakly active (IC50=106.97 µM). After the isolation of the potent AChEi huperzine A 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 [14]. Five new Lycopodium alkaloids, 11-hydroxyfawcettidine, 2,11-dihydroxyfawcettidine, 8,11-dihydroxyfawcettidine, 2-hydroxylycothunine and 8-hydroxylycothunine, with the fawcettimine skeleton were isolated from L. serratum, along with three known alkaloids, lycothunine, serratine and serratandine [8], AChE inhibitory activity was analyzed for the alkaloid lycoposerramine-H previously isolated from L. serratum, showed AChE activity [8].

Phytochemical research on Buxus hycana allowed the identification of several Buxus alkaloids with cholinesterase inhibitory activity [25]. 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 (IC50 = 28 µg/mL). The phytochemical study of this extract yielded seven compounds 119-125 which were found to show either moderate or strong AChE inhibition [26].

### Molecular mechanisms by which natural AChEi interact with AChE

The main alkaloid found in the roots of Catharanthus roseus (L.) (Apocynaceae); Serpentine represented powerful potency against AChE inhibition (IC50=0.77µM), which was attributed to the binding of its quaternary nitrogen to an Asp residue at AChE peripheral anionic site [27]. Lai et al. [28], when evaluating alkaloids from Stemona sessilifolia (Miq.) Miq. roots (Stemonaceae) characteristic stenine B as AChEi (IC50=2.10µM) and stenine (IC50=19.8µM). The authors related the high tenine B activity to its capability to perform hydrogen bonds with Tyr130, similarly to huperzine A. The Nelumbo nucifera Gaertn. (Nelumbonaceae) leaf extract fractionation result in three aporphine-alkaloids, as promising natural AChE inhibitors [29]. Salvia spp. (Lamiaceae) have been used for centuries for its beneficial effects on memory disorders [30]. Santos et al. [29], demonstrated that the diterpene cryptotanshinone extracted from the root of Salvia miltiorrhiza Bunge is a reversible inhibitor of human AChE (IC50 = 4.09µM) and that chronic oral administration can reverse cognitive deficits induced by scopolamine in rats. Flavonoids, are recently considered a promising anti-AD source [31], due to antioxidant efficacy and minimal toxicity [29]. For example, phenolic compounds; luteolin and 3, 5-dicafeoylquinic acid, from Phagnalon saxatile Cass. (Compositae) demonstrated low AChE activity [29].

### Chemically-defined molecule as inhibitors of acetylcholinesterase enzyme

The prototype for inhibitors of AChE was tacrine, which is the first drug approved in the United States (Cognex) for AD. However, its severe side effects such hepatotoxicity and gastrointestinal upset, represent an important drawback [1]. Galanthamine, a long acting, selective, reversible and competitive AChE inhibitor, is considered to be more effective in...
the treatment of AD and to have fewer limitations [32]. Recently it has reported because of the problems of bioavailability and side-effects. Donepezil was developed to overcome the physostigmine and tacrine disadvantages [33]. Rivastigmine is a carbamimilating, pseudo irreversible acetylcholinesterase inhibitor which showed nervous system selectivity [33]. (-)-Huperzine A is a natural compound from Huperzia serrata (Thumb.) It is a promising AChE reversible and selective inhibitor with a high absorption and penetration ability a cross brain barrier. Huperzine A showed a longer time of action and higher therapeutic index than other previously reported drug [1]. In China, huperzine A has already been approved as a promising ADdrug [34]. It was found 260 chemically isolated and charters tics natural compounds found in the previous literatures, which have been demonstrated for inhibition of acetylcholinesterase. The compounds tested, which have been isolated and identified belong to the classes of alkaloids, monoterpenes, coumarins, triterpenes, flavonoids, benzenoids, diterpenes [1].

Clinical studies

Besides galantamine, huperzine A is the most clinically studied alkaloidal AChEi [29]. The huperzine A efficacy was evaluated in the medication of 447 patients with dementia impairment [35]. However, in another phase II study, the results were not conclusive on its beneficial cognitive effects for patients with moderate AD, requiring further investigation [36]. A clinical trial with Salvia officinalis L. administered to patients with mild to moderate AD for a 16-weeks period led to improved cognitive performance [29]. S. officinalis also ameliorated impairment of cognitive function in moderate to severe AD. However, authors recognized that long-term efficacy, safety and administration strategy still require further investigation [29]. The daily intake of dried extract of Crocus sativus L. (Iridaceae) (30 mg/day) markedly ameliorate cognitive abability compared to donepezil-treated patients [37].

Tables (1 and 2): Summarized same bioactive compounds, natural extracts and some other natural products.

| Bioactive Compound | Condition of Participants | Number of Subjects | Duration | Outcomes | Ref. |
|--------------------|----------------------------|--------------------|----------|----------|------|
| Vitamin D          | Mild cognitive impairment  | 8                  | 8 weeks  | Reduction of Aβ level | [38] |
| Vitamin D and memantine | Moderate AD              | 43                 | 24 weeks | Improvement of cognitive functions | [39] |
| Antioxidants       | Mild to moderate AD       | 78                 | 16 weeks | Reduction of oxidative stress | [40] |
| Vitamin E and vitamin C | AD                      | 20                 | 1 month  | Reduction of oxidative stress | [41] |
| Vitamin E and selegiline | Moderate AD              | 341                | 2 years  | Delay of AD progression | [42] |
| Vitamin E and donepezil | Mild cognitive impairment | 769                | 5 years  | No effectiveness in delaying AD progression | [43] |
| Vitamin E and selenium | Healthy patients         | 3786               | 13 years | No prevention of dementia | [44] |
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| Natural product                      | Condition                      | Duration | Effectiveness                                                                 |
|-------------------------------------|-------------------------------|---------|-------------------------------------------------------------------------------|
| DHA and eicosapentaenoic acid       | AD                            | 204     | 12 months Safe and well tolerated; No effectiveness in delaying cognitive decline |
| DHA                                | AD                            | 295     | 18 months No effectiveness in delaying cognitive decline                        |
| DHA                                | Cognitive impairments         | 485     | 24 weeks Improvement of cognitive functions                                  |
| DHA                                | Mild cognitive impairment     | 36      | 1 year Safe and well tolerated; Improvement of memory                           |
| Curcumin                           | AD                            | 34      | 6 months Safe and well tolerated                                               |
| Resveratrol                        | Mild to moderate AD           | 119     | 52 weeks Side effects; No effectiveness in reducing biomarkers levels          |
| Resveratrol                        | Mild to moderate AD           | 39      | 1 year Safe and well tolerated; No effectiveness in treat AD                   |
| Huperzine A                        | AD                            | 103     | 8 weeks Safe and well tolerated; Improvement of memory and behaviour          |
| Huperzine A                        | AD                            | 60      | 60days Safe and well tolerated; Reduction of oxidative stress                 |
| Huperzine A                        | Mild to moderate AD           | 177     | 16 weeks Safe and well tolerated; Improvement of cognitive functions          |
| Melatonin                          | AD                            | 150     | 12 weeks Improvement of memory                                                |
| Melatonin                          | AD                            | 14      | 22 to 35 months Improvement of cognitive functions                            |
| Melatonin                          | Mild cognitive impairment     | 50      | 9 to 18 months Improvement of cognitive functions                             |
| Melatonin                          | AD                            | 80      | 24 weeks Safe; Improvement of cognitive functions                             |
| Nicotine                           | AD                            | 70      | 2 weeks Improvement of perceptual and visual attentional deficits            |
| Nicotine                           | AD                            | 6       | 9 weeks Safe; Improvement of learning                                         |
| Nicotine                           |                               | 8       | 10 weeks Improvement of attention performance                                |

This table is a cited work of Andrade et al. [61].
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Table 2: Natural extracts and other natural products in clinical trials for AD therapy.

| Natural Extracts and other product | Condition of Participants          | Number of Subjects | Duration | Outcomes                                                                 | Ref. |
|-----------------------------------|------------------------------------|--------------------|----------|--------------------------------------------------------------------------|------|
| Ginkgo biloba                     | Mild to moderate dementia          | 410                | 24 weeks | Safe; Improvement of neuropsychiatric symptoms                            | [62] |
| Ginkgo biloba                     | AD or vascular dementia            | 404                | 24 weeks | Improvement of cognitive functions and functional abilities; Improvement of neuropsychiatric symptoms | [63] |
| Saffron                           | Mild to moderate AD                | 46                 | 16 weeks | Safe; Improvement of cognitive functions and memory                       | [37] |
| Lemon balm                        | Mild to moderate AD                | 40                 | 4 months | Improvement of cognition function and agitation                           | [64] |
| Green tea                         | tea Severe AD                      | 30                 | 2 months | Improvement of cognitive functions                                        | [65] |
| Papaya                            | AD                                 | 20                 | 6 months | Reduction of oxidative stress                                            | [66] |
| Sage                              | Mild to moderate AD                | 20                 | 4 months | Improvement of cognitive functions; No side effects except agitation      | [67] |
| Coconut                           | AD                                 | 44                 | 21 days  | Improvement of cognitive functions                                        | [68] |
| Apple                             | Moderate to severe AD              | 21                 | 1 month  | No improvement of cognitive functions; Improvement behavioural and psychotic symptoms; Reduction of anxiety, agitation and delusion | [69] |
| Blueberry                         | Early memory failures              | 9                  | 12 weeks | Improvement of learning; Reduction of depressive symptoms                | [70] |
| Colostrinin                       | AD                                 | The information was not provided by the authors. | 15 weeks | Improvement of cognitive and daily functions                              | [71] |

This table is a cited work of Andrade et al. [61].

Toxicological studies

A recent systematic review and meta-analysis of 43 randomized placebo-controlled clinical trials showed that AChEi improved cognitive function, global symptomatology, and functional capacity, as well as decreased patients’ mortality [72]. Amongst the natural AChEi compounds berberine and safranal show to have more advantages than disadvantages. Berberine has been reported to produce mild gastrointestinal reactions, including diarrhea and constipation, besides other less frequent side effects [73]; and safranal has toxic effects on hematological and biochemical indices, as well as induced embryonic malformation in animal’s models at high doses [74].

Remarks and perspectives

The present mini-review declared that during last year’s large number of natural plant species and their related active compounds have been identified as anti-AChE activity. It is
obtainable the applying of solventsof extracts of definite polarities, which proposed that their active compounds might contain a wide range of secondary metabolites classes. Alkaloids indisputably are the most studied class of natural AChEi, what seemly has trapped the researcher’s attention in this class when in pursuit of new potential AChEi candidates, a vision that urges to be changed. Notwithstanding, the search for secondary AD-relevant pharmacological properties, such as antioxidant, deserves experimental approaches addressing their capacity to prevent oxidants generation and oxidative damage, instead of their mere scavenging capacity. For instance, berberine and related protoberberine alkaloids have been determined for their anti-AChE activity, but no phase II research has been applied yet. Thus, the use of plant species and their related active compounds already presented, their evaluation clinically especially presented the primarily barrier to be transposed in order to increase and ameliorate the pharmacological issues of patients with AD.

Conclusion

The current review demonstrates that most of the plant extracts examined showed acetylcholinesterase inhibitory effect and they could be potentially used further for AD medication. AD is a disorder with socially negative impact and, no drugs at this moment have been progress for therapy or prevention. The existing tools only directed to adjust, regulate the disease symptoms. With the increase of average life expectancy, it is fundamental to discover and develop new molecules able to prevent and treat AD. Large number of natural products have documented to be potentially for the therapy of AD clinically or in preclinical reports. In clinical trials various compounds show to be promising against AD, in human trials. Natural compounds in earlier phases of research need further studies to uncover their therapeutic potential for AD. In particular, the species belonging to Amaryllidaceae, Apiaceous, Asteraceae, Fabaceae and Fumarase were the most studied. Since most of inhibitors of acetylcholinesterase are shown to have nitrogen, the higher efficacy of these plant extracts may be attributed to alkaloidal rich fraction, which exhibited powerful AcChE inhibitory activity. More research is needed to further explore the actions of these alkaloids in the search of promising treatment for AD.

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