Open Journal of Pharmaceutical Science and Research

Review Article   **Open Access**

Natural products and their derived compounds inhibitors of the enzyme acetylcholinesterase

Maha Z. Rizk and Hanan F. Aly

Department of Therapeutic Chemistry, Pharmaceutical and Drug Industries Research Division, National Research Centre (N.R.C.) 33 El Bohouth St., Dokki, Giza, P.O. 12622, Egypt

*Corresponding Author: Maha Z. Rizk: maha_zaki_rizk@yahoo.com; Hanan F. Aly: hanan_abduallah@yahoo.com

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

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 synapsis 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

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-pyrano [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 Ki = 110.0, 30.0 and 30.0 μM, 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 benzylisoquin oline alkaloids with anti-AChE activity [14]. C. turtschaninovii ethanolic extract 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 charterstics in Coptis chinensisrhizomes are used for the medication of different disorders in Chinese folk medicine. Six protoberberine alkaloids were identified in rhizomes of Coptis chinensis which are traditionally used in Chinese medicine for the treatment of various diseases. Also, rhizomesof coptidis and their active alkaloids were found to have cognitive-stimulating and neuro-protective function [16]. The anti-AChE activity of these alkaloids showed that the IC50 values of berberine, palmatine, jateorrhizine, coptisine and groenlandicine ranged between 0.44 and 0.80 μM while that of epiberberine was slightly higher (IC50 = 1.07 μM) [16]. Groenlandicine and berberine were found to have BChE inhibitory activity and epiberberine was reported tomarkedly inhibited beta-secretase (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* (Menispermaceae), wasreported tohave AChE inhibitory activity. The ethanolic extract of *S. venosa* was subjected to bioassay-guided fractionation to identify AChEi [18]. A typical fractionationtools wasapplied toknow 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 monoterpenoid 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 4.4μM, respectively, these values being similar to that of galanthamine (3.2 μM). On the other hand, 10-hydro- xycoronaridine 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 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 crudeextract of T. *divaricata*root was reported toproduce 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, 11hydroxyvittatine, 8-O-demethylmaritidine and vittatine as well as the new alkaloid 11beta-hydro- xy 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 11hydroxyvittatine [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-dihydro-xyfawcettidine, 2-hydroxylycothunine and 8hydroxylycothunine , with the fawcettimine skeleton were isolated from *L. serratum*, along with three known alkaloids, lycothunine, serratine and serratanidine [8], AChE inhibitory activity was analyzed for the alkaloid lycoposerramine-H previously isolated from L. serratum ,showed Achi [8].

Phytochemical research on Buxus hyrcana 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 itscapability toperform 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 considereda promising anti-AD source [31], due to antioxidantefficacy and minimal toxicity [29]. For example, phenolic compounds; luteolin and 3, 5-dicaffeoylquinic 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. Donezepil was developed to overcome the physostigmine and tacrine disadvantages [33]. Rivastigmine is a carbamilating, 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 eability compared to donepezil-treated patients [37].

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

Table 1: Bioactive compounds in clinical trials for AD therapy.

Bioactive Compound	Condition of Participants	Number of Subjects	Duration	Outcomes	Ref.
Vitamin D	Mildcognitive 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]

Docosahexaenoic acid (DHA) and eicosapentaenoic acid	AD	204	12 months	Safe and well tolerated; No effectiveness in delaying cognitive decline	[45]
DHA	AD	295	18 months	No effectiveness in delaying cognitive decline	[46]
DHA	Cognitive impairments	485	24 weeks	Improvement of cognitive functions	[47]
DHA	Mild cognitive impairment	36	1 year	Safe and well tolerated; Improvement of memory	[48]
Curcumin	AD	34	6 months	Safe and well tolerated	[49]
Resveratrol	Mild to moderate AD	119	52 weeks	Side effects; No effectiveness in reducing biomarkers levels	[50]
Resveratrol	Mild to moderate AD	39	1 year	Safe and well tolerated; No effectiveness in treat AD	[51]
Huperzine A	AD	103	8 weeks	Safe and well tolerated; Improvement of memory and behaviour	[52]
Huperzine A	AD	60	60days	Safe and well tolerated; Reduction of oxidative stress	[53]
Huperzine A	Mild to moderate AD	177	16 weeks	Safe and well tolerated; Improvement of cognitive functions	[36]
Melatonin	AD	150	12 weeks	Improvement of memory	[54]
Melatonin	AD	14	22 to 35	months Improvement of cognitive functions	[55]
Melatonin	Mild cognitive impairment	50	9 to 18 months	Improvement of cognitive functions	[56]
Melatonin	AD	80	24 weeks	Safe; Improvement of cognitive functions	[57]
Nicotine	AD	70	2 weeks	Improvement of perceptual and visual attentional deficits	[58]
Nicotine	AD	6	9 weeks	Safe; Improvement of learning	[59]
Nicotine		8	10 weeks	Improvement of attention performance	[60]

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

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 tohave more advantages than disadvantages. Berberine has been reported toproduce 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

observable 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 AchE inhibitory activity. More research is needed to further explore the actions of these alkaloids in the search of promising treatment for AD.

References

1. Barbosa-Filho JMB, Medeiros KCP, Diniz MFM, et al. 2006. Natural products inhibitors of the enzyme acetylcholinesterase. Brazilian Journal of Pharmacognosy. 16: 258-285. Ref.: https://bit.ly/2SM82yU

2. Howes MJR, Perry NSL, Houghton PJ. 2003. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. Phytother Res. 17: 1-18. Ref.: https://bit.ly/3blgPhw

3. Johnson N, Davis T, Bosanquet N. 2000. The epidemic of Alzheimer's disease; how can we manage the costs? Pharmacoeconomics. 18: 215-223. Ref.: https://bit.ly/3fEnvuL

4. Zarotsky V, Sramek JJ, Cutler NR. 2003. Galanthamine hydrobromide: an agent for Alzheimer's disease. Am J Health-System Pharmacist. 60: 446-452. Ref.: https://bit.ly/2xJSlke

5. Bruhlmann C, Ooms F, Carrupt PA, et al. 2001. Coumarin derivatives as dual inhibithors of acetylcholinesterase and monoamine oxidase. J Med Chem. 44: 3195-3198. Ref.: https://bit.ly/3fwMzDN

6. Morais LCSL, Barbosa-Filho JM, Almeida RN. 2003. Plants and bioactives compounds for the treatment of Parkinson's desease. Arquivo de Fitomedicina. 1: 127132. Ref.: https://bit.ly/2SSj1H4

7. Rocha LG, Almeida JRGS, Macedo RO, et al. 2005. A review of natural products with antileishmanial activity. Phytomedicine. 12: 514-535. Ref.: https://bit.ly/2znB9lf

8. Murraya AP, Faraonia MB, Castroa MJ, et al. 2013. Natural AChE Inhibitors from Plants and their Contribution to Alzheimer's Disease

Therapy.Current Neuropharmacology.11: 388-413. Ref.: https://bit.ly/2SPK9Gr

9. Viegas-Junior C, Bolzani VS, Furlan M, et al. 2004. Produtos naturais como candidatos a fármacos úteis no tratamento do mal de Alzheimer. Quim Nova. 27: 655-660. Ref.: https://bit.ly/2YNnEpF

10. Trevisan MTS, Macedo FVV. 2003. Seleção de plantas com atividade anticolinesterase para tratamento da doença de Alzheimer. Quim Nova. 26: 301-304. Ref.: https://bit.ly/3bjmKUc

11. Rahman AU, Khalid A, Sultana N, et al. 2006. New natural cholinesterase inhibiting and calcium channel blocking quinoline alkaloids. J. Enzyme Inhib. Med. Chem. 21: 703-710. Ref.: https://bit.ly/3fwNhRt

12. Yang Z, Zhang D, Ren J, et al. 2012. Skimmianine, a furoquinoline alkaloid from Zanthoxylum nitidum as a potential acetylcholinesterase inhibitor. Med. Chem. Res. 21: 722-725. Ref.: https://bit.ly/2WCSZbW

13. Mukherjee PK, Mukherjee D, Maji AK, et al. 2009. The sacred lotus (Nelumbo nucifera) - phytochemical and therapeutic profile. J. Pharm. Pharmacol. 61: 407-422. Ref.: https://bit.ly/2YJA8hX

14. Houghton PJ, Ren Y, Howes MJ. 2006. Acetylcholinesterase inhibitors from plants and fungi. Nat. Prod. Rep. 23: 181199. Ref.: https://rsc.li/2SMEsJi

15. Hung TM, Na M, Dat NT, et al. 2008. Cholinesterase inhibitory and antiamnesic activity of alkaloids from Corydalis turtschaninovii. J. Ethnopharmacol. 119: 74-80. Ref.: https://bit.ly/3dviYJ8

16. Jung HA, Min BS, Yokozawa T, et al. 2009. Anti-Alzheimer and antioxidant activities of Coptidis Rhizoma alkaloids. Biol. Pharm. Bull. 32: 1433-1438. Ref.: https://bit.ly/2SOyPKO

17. Chlebek J, Macáková K, Cahlíkovi L, et al. 2011. Acetylcholinesterase and butyrylcholinesterase inhibitory compounds from Corydalis cava (Fumariaceae). Nat. Prod. Commun. 6: 607-610. Ref.: https://bit.ly/2SMEC3m

18. Ingkaninan K, Phengpa P, Yuenyongsawad S, et al. 2006. Acetylcholinesterase inhibitors from Stephania venosa tuber. J. Pharm. Pharmacol. 58: 695-700. Ref.: https://bit.ly/2xLPoQc

19. Cho KM, Yoo ID, Kim WG. 2006. 8-Hydroxydihydrochelerythrine and 8-Hydroxydihydrosanguinarine with a potent acetylcholinesterase inhibitory activity from Chelidonium majus L. Biol. Pharm. Bull. 29: 2317-2320. Ref.: https://bit.ly/2yFveYF

20. Zhan ZJ, Yu Q, Wang ZL, et al. 2010. Indole alkaloids from Ervatamia hainanensis with potent acetylcholinesterase inhibition activities. Bioorg. Med. Chem. Lett. 20: 6185-6187. Ref.: https://bit.ly/2SOV5UU

21. Andrade MT, Lima JA, Pinto AC, et al. 2005. Indole alkaloids from Tabernaemontana australis (Muell. Arg) Miers that inhibit acetylcholinesterase enzyme. Bioorg. Med. Chem. 13: 4092-4095. Ref.: https://bit.ly/2WJh0hz

22. Seidl C, Correia BL, Stinghen AE, et al. 2010. Acetylcholinesterase inhibitory activity of uleine from Himatanthus lancifolius. Z. Naturforsch. C. 65: 440-444. Ref.: https://bit.ly/2SJwr8b

23. de Andrade JP, Berkov S, Viladomat F, et al. 2011. Alkaloids from Hippeastrum papillo. Molecules. 16: 7097-7104. Ref.: https://bit.ly/2xNl1c9

24. Sarikaya BB, Kaya GI, Onur MA, et al. 2012. Alkaloids from Galanthus rizehensis. Phytochem. Lett. 5: 367-370. Ref.: https://bit.ly/3bia93V

25. Ata A. 2012. In Studies in Natural Products Chemistry, 1st Edition, Rahman, A.U. Ed. Elsevier B.V.: Amsterdam. 225245.

26. Matochko WL, James A, Lam CW, et al. 2010. Triterpenoidal alkaloids from Buxus natalensis and their acetylcholinesterase inhibitory activity. J. Nat. Prod. 73: 1858-1862. Ref.: https://bit.ly/35HoDZV

27. Pereira DM, Ferreres F, Oliveira, JM, et al. 2010. Pharmacological effects of Catharanthus roseus root alkaloids in acetylcholinesterase inhibition and cholinergic neurotransmission.

Phytomedicine. 17: 646-652. Ref.: https://bit.ly/2LcufBT

28. Lai DH, Yang ZD, Xue WW. et al. 2013. Isolation, characterization and acetylcholinesterase inhibitory activity of alkaloids from roots of Stemona sessilifolia. Fitoterapia. 89: 257-264. Ref.: https://bit.ly/2SPuAi0

29. Santos TC, Gomes TM, Pinto BAS, et al. 2018. Naturally Occurring Acetylcholinesterase Inhibitors and Their Potential Use for Alzheimer's Disease Therapy. Front. Pharmacol. 9: 1192. Ref.: https://bit.ly/2WCCNY0

30. Hamidpour M, Hamidpour R, Hamidpour S, et al. 2014. Chemistry, pharmacology, and medicinal property of sage (Salvia) to prevent and cure illnesses such as obesity, diabetes, depression, dementia, lupus, autism, heart disease, and cancer. J. Tradit. Complement. Med. 4: 82-88. Ref.: https://bit.ly/35IZLkt

31. Khan H, Amin S, Kamal MA, et al. 2018. Flavonoids as acetylcholinesterase inhibitors: current therapeutic standing and future prospects. Biomed. Pharmacother. 101: 860-870. Ref.: https://bit.ly/2LadgQN

32. Rhee IK, Appels N, Luijendijk T, et al. 2003. Determining acetylcholinesterase inhibitory activity in plant extract using a fl uorimetric fl ow assay. Phytochem Anal. 14: 145-149. Ref.: https://bit.ly/2AdMm8j

33. Racchi M, Mazzucchelli M, Porrello E, et al. 2004. Acetylcholinesterase inhibitors: novel activities of old molecules. Pharmacol Res. 50: 441-451. Ref.: https://bit.ly/2SRx7bH

34. Hogenauer K, Baumann K, Enz A, et al. 2001. Synthesis and acetylcholinesterase inhibition of 5desaminohuperzine A derivatives. Bioorg Med Chem Lett. 11: 2627-2630. Ref.: https://bit.ly/2YYK1Zp

35. Ma X, Tan C, Zhu D, et al. 2007. Huperzine A from Huperzia species-an ethnopharmacological review. J. Ethnopharmacol. 113: 15-34. Ref.: https://bit.ly/3dGwauT

36. Rafii M, Walsh S, Little J, et al. 2011. A phase II trial of huperzine A in mild to moderate Alzheimer disease. Neurology. 76: 1389-1394. Ref.: https://bit.ly/3ck7jMV

37. Akhondzadeh S, Shafiee Sabet M, Harirchian MH, et al. 2010. A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. Psychopharmacology. 207: 637-643. Ref.: https://bit.ly/2LaqfBZ

38. Miller BJ, Whisner CM, Johnston CS. 2016. Vitamin D Supplementation Appears to Increase Plasma Aβ 40 in Vitamin D Insufficient Older Adults: A Pilot Randomized Controlled Trial. J. Alzheimer's Dis. 52: 843-847. Ref.: https://bit.ly/35Mavyg

39. Annweiler C, Herrmann FR, Fantino B, et al. 2012. ectiveness of the Combination of Memantine Plus Vitamin D on Cognition in Patients With Alzheimer Disease: A Pre-Post Pilot Study. Cogn. Behav. Neurol. 25: 121-127. Ref.: https://bit.ly/2YLOiyZ

40. Galasko DR, Peskind E, Clark CM. et al. 2012. Antioxidants for alzheimer disease: Arandomized clinical trial with cerebrospinal fluid biomarker measures. Arch. Neurol. 69: 836-841. Ref.: https://bit.ly/2YNnD4M

41. Kontush A, Mann U, Arlt S, et al. 2001. Influence of vitamin E and C supplementation on lipoprotein oxidation in patients with Alzheimer's disease. Free Radic. Biol. Med. 31: 345-354. Ref.: https://bit.ly/3dxgTMu

42. Sano M, Ernesto C, Thomas RG, et al. 1997. A Controlled Trial of Selegiline, Alpha-Tocopherol, or Both as Treatment for Alzheimer's disease. N. Engl. J. Med. 336: 1216-1222. Ref.: https://bit.ly/2Lcvukv

43. Petersen RC, Thomas RG, Grundman M, et al. 2005. Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment. N.Engl. J.Med. 352: 2379-2388. Ref.: https://bit.ly/2LeUasQ

44. Kryscio RJ, Abner EL, Caban-Holt A, et al. 2017. Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). JAMA Neurol. 74: 567-573. Ref.: https://bit.ly/2WiQsVf

45. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. 2006. ω-3 Fatty Acid Treatment in 174 Patients with Mild to Moderate Alzheimer Disease: Omeg AD Study: A Randomized Double-blind Trial. Arch. Neurol. 63: 1402-1408. Ref.: https://bit.ly/2YQWJJp

46. Quinn JF, Raman R, Thomas RG, et al. 2010. Docosahexaenoic Acid Supplementation and Cognitive Decline in Alzheimer Disease: A Randomized Trial. JAMA. 304: 1903-1911. Ref.: https://bit.ly/2zqsyhn

47. Yurko-Mauro K, McCarthy D, Rom D, et al. 2010. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimer's Dement. 6: 456-464. Ref.: https://bit.ly/2LeVgEI

48. Lee LK, Shahar S, Chin AV, et al. 2013. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): A12-monthrandomised, double-blind, placebo-controlled trial. Psychopharmacology. 225: 605-612. Ref.: https://bit.ly/2WefHYG

49. Baum L, Lam CWK, Cheung SKK, et al. 2008. Six-Month Randomized, Placebo-Controlled, Double-Blind, Pilot Clinical Trial of Curcumin in Patients with Alzheimer Disease. J. Clin. Psychopharmacol. 28: 110-113. Ref.: https://bit.ly/2zmB8xW

50. Turner RS, Thomas RG, Craft S, et al. 2015. Arandomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. Neurology. 85: 1383-1391. Ref.: https://bit.ly/2WJAF0A

51. Zhu CW, Grossman H, Neugroschl J, et al. 2018. Arandomized, double-blind, placebo-controlled trial of resveratrol with glucose and malate (RGM)to slow the progression of Alzheimer's disease: A pilot study. Alzheimer's Dement. Transl. Res. Clin. Interv. 4: 609-616. Ref.: https://bit.ly/2yxEi1T

52. Xu SS, Gao ZX, Weng Z, et al. 1995. cacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li Xue Bao. 16: 391-395. Ref.: https://bit.ly/2SJB567

53. Xu SS, Cai ZY, Qu ZW, et al. 1999. Huperzine-A in capsules and tablets for treating patients with Alzheimer disease. Zhongguo Yao Li Xue Bao. 20: 486-490. Ref.: https://bit.ly/3dtopbl

54. Brusco LI, Márquez M, Cardinali DP. 1998. Monozygotic twins with Alzheimer's disease treated with melatonin: Case report. J. Pineal Res. 25: 260-263. Ref.: https://bit.ly/3fzNXpe

55. Brusco LI, Marquez M, Cardinali DP. 2000. Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer's disease. Neuro Endocrinol. Lett. 21: 39-42. Ref.: https://bit.ly/2YI7hKW

56. Furio AM. Brusco LI. Cardinali DP. 2007. Possible the rapeutic value of melatonin in mild cognitive impairment: A retrospective study. J. Pineal Res. 43: 404-409. Ref.: https://bit.ly/2YLSVJq

57. Wade AG, Farmer M, Harari G, et al. 2014. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: A 6-month, randomized, placebo-controlled, multicenter trial. Clin. Interv. Aging. 9: 947-961. Ref.: https://bit.ly/3dsRHXG

58. Jones GM, Sahakian BJ, Levy R, et al. 1992. effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. Psychopharmacol. 108: 485-494. Ref.: https://bit.ly/3bhrlGv

59. WilsonAL, Langley LK, Monley J, et al. 1995. Nicotine patches in Alzheimer's disease: Pilot study on learning, memory, and safety. Pharmacol. Biochem. Behav. 51: 509-514. Ref.: https://bit.ly/2SNYYJO

60. White HK, Levin ED. 1999. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology (Berl). 143: 158-165. Ref.: https://bit.ly/2WiS29D

61. Andrade S, Ramalho M J, Loureiro JA, et al. 2019. 'Natural Compounds for Alzheimer's Disease Therapy: A Systematic Review of Preclinical and Clinical Studies'. International journal of molecular sciences. 2313. DOI: 10.3390/ijms20092313; Ref.: https://www.mdpi.com/1422-0067/20/9/2313

62. Bachinskaya N, Hoerr R. IHl R. 2011. Alleviatingneuropsychiatricsymptomsindementia: Thee effects of Ginkgo biloba extract EGb 761. Findings from a randomized controlled trial. Neuropsychiatr. Dis. Treat. 7: 209-215. Ref.: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3090284/

63. Ihl R, Tribanek M, Bachinskaya N. 2012. Efficacy Formulation of Ginkgo biloba Extract EGb761® in Alzheimer's Disease and Vascular Dementia: Results from a Randomised Controlled Trial. Pharmacopsychiatry. 45: 41-46. Ref.: https://bit.ly/2WLDZIS

64. Akhondzadeh S, Noroozian M, Mohammadi M, et al. 2003. Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomised, placebo controlled trial. J. Neurol. Neurosurg. Psychiatry. 74: 863-866. Ref.: https://bit.ly/2AdONrt

65. Arab H, Mahjoub S, Hajian-Tilaki K, et al. 2016. The effect of green tea consumption on oxidative stress marker s and cognitive function in patients with Alzheimer's disease: A prospective intervention study. CASP J. Int. Med.75: 188-194. Ref.: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5062177/

66. Barbagallo M. Marotta F, Dominguez LJ. 2015. Oxidative stress in patients with Alzheimer's disease: effect of extracts of fermented papaya powder. Mediat. Inflamm.

67. Scholey AB,Tildesley NT, Ballard CG, et al. 2008. An extract of Salvia (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers. Psychopharmacology (Berl). 198: 127-139. Ref.: https://bit.ly/3fxWQja

68. De la Rubia Orti JE, Garcia-Pardo MP, Drehmer E, et al. 2018. Improvement of Main Cognitive Functions in Patients with Alzheimer's Disease after Treatment with Coconut Oil Enriched Mediterranean Diet: APilot Study. J. Alzheimers Dis. 65: 577-587. Ref.: https://bit.ly/3dAKzst

69. Remington R, Chan A, Lepore A, et al. 2010. Apple juice improved behavioral but not cognitive symptoms in moderate-to-late stage Alzheimer's disease in an open-label pilot study. Am. J. Alzheimers Dis. Dement. 25: 367-371. Ref.: https://bit.ly/2LfTSSu

70. Krikorian R, Shidler MD, Nash TA, et al. 2010. Joseph, J.A. Blueberry supplementation improves memory in older adults. J. Agric. Food Chem. 58: 3996-4000. Ref.: https://bit.ly/3chuIid

71. Szaniszlo P, German P, Hajas G, et al. 2009. Boldogh, I. New insights into clinical trial for Colostrinin in Alzheimer's disease. J. Nutr. Health Aging. 13: 235-241. Ref.: https://bit.ly/3ds9PRs

72. Blanco-Silvente L, Castells X, Saez M, et al. 2017. Discontinuation, Efficacy, and safety of cholinesterase inhibitors for Alzheimer's disease: a meta-analysis and metaregression of 43 randomized clinical trials enrolling 16 106 patients. Int. J. Neuropsychopharmacol. 20: 519-528. Ref.: https://bit.ly/3ds6lOT

73. Bostan HB, Mehri S, Hosseinzadeh H. 2017. Toxicology effects of saffron and its constituents: a review. Iran J. Basic Med. Sci. 20: 110-121. Ref.: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5339650/

74. Imenshahidi M, Hosseinzadeh H. 2016. Berberis vulgaris and berberine: an update review. Phytother. Res. 30: 1745-1764. Ref.: https://bit.ly/2WGq1Yv