Medicinal plants with cholinesterase inhibitory activity and their applications

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Abstract

Cholinesterase catalyzes the hydrolysis of acetylcholine in the synapse, into choline and acetic acid, a reaction necessary to return the cholinergic neuron in the central and peripheral nervous systems, to the resting potential after activation. The cholinesterase enzyme inactivation, or inhibition induced by various inhibitors, leads to accumulation of acetylcholine, and subsequent hyper-stimulation of nicotinic and muscarinic receptors. Hence, acetylcholinesterase inhibitors, are applied as relevant drugs and toxins. The current review highlighted the medicinal plants with cholinesterase inhibitory effects.

Keywords: Cholinesterase; Inhibition; Medicinal Plants; Pharmacology; Therapeutic

1. Introduction

Cholinesterase catalyzes the hydrolysis of acetylcholine in the synapse, into choline and acetic acid, a reaction necessary to return the cholinergic neuron in the central and peripheral nervous systems, to the resting potential after activation. There are two types of cholinesterases; acetylcholinesterase which found in nerve and muscle, central and peripheral tissues, motor and sensory fibers, and cholinergic and noncholinergic fibers (1-2), In addition to pseudo cholinesterase (plasma cholinesterase, butyryl cholinesterase) which found primarily in the liver (3).

The cholinesterase enzyme inactivation, or inhibition induced by various inhibitors, leads to accumulation of acetylcholine, and subsequent hyper-stimulation of nicotinic and muscarinic receptors. Hence, acetyl cholinesterase inhibitors, are applied as relevant drugs and toxins. Some of reversible and irreversible AChE inhibitors were applied in pharmacology in Alzheimer's disease, Parkinson's disease, myasthenia gravis and glaucoma (2). Many previous pharmacological studies revealed that the medicinal plants possessed cholinesterase inhibitory effects and were tested in Alzheimer's disease and memory deficits and as anti-Parkinsonian(4-8).

The current review was performed to highlight the medicinal plants with cholinesterase inhibitory effects.

2. Medicinal plants with cholinesterase inhibitory activity

2.1. Bellis perennis

Apigenin-7-O-ghicopyranoside (ApG), a flavonoid isolated from the flowers of Bellis perennis L., showed strong in vitro antioxidant potential, because of the capacity of removal of hydroxyl radicals and nitric oxide, and also prevented the formation of thiobarbituric acid-reactive substances. These parameters were inhibited at the highest concentration of ApG at rates of 77.7%, 72% and 73.4%, respectively, in addition, its inhibitory effect on acetyl cholinesterase, suggesting potential use in the treatment of neurodegenerative diseases(9-10).

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2.2. *Canna indica*

Sub lethal *in vivo* 24 h exposure to (40% and 80% of 24 h LC50) active fractions of *Canna indica* root, significantly inhibited the activity of acetyl cholinesterase, acid/alkaline phosphatase, Na+K+ATPase and lactic dehydrogenase in the nervous tissue of *Lynnaea acuminata*. The inhibition kinetics of these enzymes indicated that active fractions of the plants caused a competitive inhibition of AChE, LDH, ALP, ACP and Na+K+ATPase (11-12).

2.3. *Capsella bursa-pastoris*

Evaluation of acetylcholinesterase inhibition of the *Capsella bursa-pastoris* extracts revealed that these extracts were moderate acetyl cholinesterase inhibitors (13-14).

2.4. *Cichorium intybus*

The efficacy of *Cichorium intybus* leaves powder to minimize the oxidative damage, causing brain dysfunction in diabetes, was studied in rats. Diabetes was induced with alloxan monohydrate. Oxidative damage, impairment of oxidative defense and neuronal activity were investigated in cerebral hemispheres 48 h after alloxan administration. Diabetes caused an elevation (p<0.001) of blood glucose, protein carbonyl content (PrC) and lipid peroxidation. The brain level of the antioxidant enzyme, catalase (CAT), reduced glutathione (GSH) and acetyl cholinesterase (AChE) exhibited significant decline in alloxan-diabetes. Feeding with dried powder leaves of *Cichorium intybus* decreased blood glucose level to near normal level and minimize the impairment of oxidative defense (15-16).

2.5. *Cistanche tubulosa*

The ameliorating effects of *Cistanche tubulosa* extract which was quantified with three phenylpropanoid glycosides was studied in Alzheimer's disease (AD)-like rat model. Amyloid β peptide 1-42 (Aβ 1-42) intra-cisternally infused rats by osmotic pump was used as an AD-like rat model. The major pathological makers were measured including Aβ 1-42 immuno-histochemical stain, behavioral tests (inhibitory avoidance task and Morris water maze) and central neurotransmitter functions. Aβ 1-42 caused cognitive deficits, increased amyloid deposition and acetylcholine esterase activities, and decreased levels of brain’s acetylcholine and dopamine. Daily administration of *Cistanche tubulosa* extract throughout Aβ 1-42 infusion periods ameliorated the cognitive deficits, decreased amyloid deposition and reversed cholinergic and hippocampal dopaminergic dysfunction caused by Aβ 1-42(17-18).

2.6. *Citrus aurantifolia*

The anti-cholinesterase activity of *Citrus aurantifolia* peel and leaves from different areas of growth, was studied. *N*-Hexane fractions of both peel and leaves showed a good acetyl cholinesterase inhibitory activity with IC50 values in the range 91.4-107.4 μg/ ml (19-20).

2.7. *Clitoria ternatea*

The effectiveness of alcoholic extracts of aerial and root parts of *Clitoria ternatea* at 300 and 500 mg/kg doses orally was studied in attenuating electroshock-induced amnesia in rats. Extracts at 300 mg/kg dose produced significant memory retention, and the root parts were found to be more effective. In order to delineate the possible mechanism through which *Clitoria ternatea* elicited the anti-amnesic effects, its influence on central cholinergic activity was studied by estimating the acetylcholine content of the whole brain and acetyl cholinesterase activity at different regions of the rat brain (cerebral cortex, midbrain, medulla oblongata and cerebellum). The results showed that *Clitoria ternatea* extracts increase rat brain acetylcholine content and acetyl cholinesterase activity, in a similar fashion to the standard cerebro-protective drug, Pyritinol(21-22).

2.8. *Colchicum balansae*

Methanol extracts of the seeds of *Colchicum balansae* were investigated for their *in vitro* cholinesterase (AChE and BChE) inhibitory activity at 200 μg/ml using ELISA microplate assay. Acetyl cholinesterase inhibitory activity possessed by the methanolic extracts of *Colchicum balansae* seeds extract (200μg/ml) was 10.90 ± 1.17% and BChE inhibitory activity was 44.22 ± 2.46% (23).

Many authors mentioned that acetyl cholinesterase inhibitors are the most effective approach to treat the cognitive symptoms of Alzheimer’s disease. Although acetyl cholinesterase inhibitors was the most widely used medication in Alzheimer’s disease treatment, but some report propound that acetyl cholinesterase inhibitors have inclement side effects such as anorexia, diarrhoea, fatigue, nausea, muscle cramps as well as gastrointestinal, cardio-respiratory,
genitourinary and sleep disturbances. Accordingly, medical field search for new acetyl cholinesterase inhibitors with higher efficacy from natural sources. *Colchicum balansae* is one of the promising sources (24-26).

2.9. Coriandrum sativum

The effects of fresh *Coriandrum sativum* leaves (CSL) on cognitive functions, total serum cholesterol levels and brain cholinesterase activity was investigated in mice. CSL (5, 10 and 15% w/w of diet) was fed orally with a specially prepared diet, for 45 days consecutively to mice. Elevated plus-maze and passive avoidance apparatus were used as the exteroceptive behavioral models for testing memory. Diazepam, scopolamine and ageing-induced amnesia were used as the interoceptive behavioral models. CSL (5, 10 and 15% w/w of diet) produced a dose-dependent improvement in memory scores of young as well as aged mice. CSL also reversed successfully the memory deficits induced by scopolamine (0.4 mg/kg, ip) and diazepam (1 mg/kg, ip). Brain cholinesterase activity and serum total cholesterol levels were considerably reduced by CSL administration in daily diets for 45 days (27-29).

2.10. Cressa cretica

The effects of *Cressa cretica* was evaluated in learning and memory in mice. Elevated plus maze and passive avoidance paradigm were utilized to test learning and memory. Two doses (200 and 400 mg/kg, po) of ethanolic extract were administered for 28 successive days in separate group of animals. The dose of 400 mg/kg po, of *Cressa cretica* extract (CCE) significantly improved learning and memory of mice. Furthermore, this dose significantly reversed the amnesia induced by scopolamine (0.4 mg/kg, ip). To find out the mechanism by which CCE exerted nootropic activity, the effect of CCE on whole brain AChE activity was also estimated. CCE decreased whole brain acetyl cholinesterase activity and reduced whole brain MDA and NO levels. The antioxidant properties and the presence of flavonoids in *Cressa cretica* may be contributing to memory enhancement effect. Accordingly, *Cressa cretica* was a potent candidate for enhancing learning and memory and it would be beneficial for the treatment of amnesia and Alzheimer’s disease (30-32).

2.11. Crocus sativus

Inhibitors of acetylcholine breakdown by acetyl cholinesterase (AChE) constituted the main therapeutic modality for Alzheimer’s disease. The inhibition of AChE activity of saffron extract and its constituents was studied by in vitro enzymatic and molecular docking studies. Saffron extract showed moderate AChE inhibitory activity (up to 30%), but IC₅₀ values of crocetin, dimethylcrocetin, and safranal were 96.33, 107.1, and 21.09 μM, respectively. Kinetic analysis showed mixed-type inhibition, which was verified by in silico docking studies. Safranal interacted only with the binding site of the AChE, but crocetin and dimethylcrocetin bind simultaneously to the catalytic and peripheral anionic sites (33-34).

2.12. Cupressus sempervirens

The dichloromethane, acetone, ethyl acetate, and methanol extracts of the cones and leaves of *Cupressus sempervirens* var. *horizontalis* (CSH) and var. *pyramidalis* (CSP) were screened for their inhibitory activity against acetyl cholinesterase (AChE), butyryl cholinesterase (BChE), and tyrosinase (TYRO). The extracts displayed weak to moderate cholinesterase inhibition at 200 μg/ml. The cone dichloromethane extract of CSP showed the highest inhibition (36.10±1.45%) against AChE, while the best inhibition (40.01±0.77%) against BChE was caused by the leaf acetone extract of CSH (35).

The anti-acetyl cholinesterase activity of *Cupressus sempervirens* essential oil was investigated. It showed that essential oil inhibitory concentration (IC₅₀) was 0.2837 ± 0.0115 mg/ml (36-37).

2.13. Cymbopogon schoenanthus

The acetyl cholinesterase inhibitory activity of the essential oils from fresh leaves, dried leaves and roots of *Cymbopogon schoenanthus* was investigated. The greatest acetyl cholinesterase inhibitory activity (IC₅₀ = 0.26 ± 0.03 mg/ml) was exhibited by the essential oil of the fresh leaves from the mountain region in southern Tunisia (38).

Aqueous extract, proanthocyanidin rich extract, and organic extracts of *Cymbopogon schoenanthus* shoots from three different locations in south Tunisia were screened for acetyl cholinesterase inhibitory activity. The greatest acetyl cholinesterase inhibitory activity (IC₅₀ = 0.23±0.04mg/ml) was exhibited by the ethyl acetate and methanol extracts of the plants collected from the mountainous region in Tunisia (39-40).
2.14. *Dalbergia sissoo*

The effect of ethanolic leaf extracts of *Dalbergia sissoo* (ELDS) on learning and memory activity was evaluated in mice. ELDS was given as 300, 450, and 600 mg/Kg respectively. The effect of ethanolic leaf extract of *Dalbergia sissoo* was investigated in mice for memory enhancing activity using various experimental paradigms of learning and memory (Transfer latency (TL) on elevated plus maze and passive avoidance). For memory and learning activity vehicle / extracts / STD drug administered daily for first seven days, on 8th day dementia was induced by scopolamine. ELDS significantly enhanced the learning and memory activities against the scopolamine induced dementia and significant decrease in acetyl cholinesterase level in brain in animals. The memory enhancement activity was due to cholinergic facilitatory effect in animals [41-42],

2.15. *Datura Species*

Because of the central nervous system effects of the belladonna alkaloids, the patient may be agitated, combative, confused, and disoriented. Initial intervention focuses on addressing those issues that protect the patient and their caregivers. In severe cases, physostigmine, a cholinesterase inhibitor, should be used to reverse anti-cholinergic toxicity. Physostigmine should be given intravenously to an adult in a dose of 0.5–2.0 mg at a rate of no more than 1 mg/min; a second dose may be administered if necessary. Children should receive 0.02 mg/kg intravenously and the rate should not exceed 0.5 mg/min [43-44],

2.16. *Daucus carota*

The effects of ethanolic extract of *Daucus carota* seeds on cognitive functions, total serum cholesterol levels and brain cholinesterase activity were studied in mice. The ethanolic extract of *Daucus carota* seeds (DCE) was administered orally in three doses (100, 200, 400 mg/kg) for seven successive days to different groups of young and aged mice. Elevated plus maze and passive avoidance apparatus was used as exteroceptive behavioral models for testing memory. Diazepam-, scopolamine- and ageing-induced amnesia were used as interoceptive behavioral models. DCE (200, 400 mg/kg, po) showed significant improvement in memory scores of young and aged mice. The extent of memory improvement evoked by DCE was 23% at the dose of 200 mg/kg and 35% at the dose of 400 mg/kg in young mice using elevated plus maze. Significant improvements in memory scores were observed with the using passive avoidance apparatus and aged mice. DCE also reversed the amnesia induced by scopolamine (0.4 mg/kg, ip) and diazepam (1 mg/kg, ip). *Daucus carota* extract (200, 400 mg/kg, po) significantly reduced the brain acetyl cholinesterase activity and cholesterol levels in young and aged mice. The extent of inhibition of brain cholinesterase activity evoked by DCE at the dose of 400 mg/kg was 22% in young and 19% in aged mice. There was a remarkable reduction in total cholesterol level as well, to the extent of 23% in young and 21% in aged animals with this dose of DCE [45-46],

2.17. *Eschscholzia californica*

The roots and aerial parts of *Eschscholzia californica* were extracted with ethanol, column chromatography, preparative TLC, and crystallization. Fourteen isoquinoline alkaloids were isolated from the ethanolic extract of the roots and aerial parts of *Eschscholzia californica*. All isolated compounds were tested for human blood acetyl cholinesterase (HuAChE) and human plasma butyryl cholinesterase (HuBuChE) inhibition activity. None of the compounds isolated significantly inhibited both HuAChE and HuBuChE, but two benzylisoquinoline alkaloids showed inhibitory activity against HuBuChE [47-48],

2.18. *Ficus carica*

The n-hexane, chloroform, acetone, methanol, n-butanol, and water extracts of the leaves of *Ficus carica var. domestica* were screened for their cholinesterase inhibitory effect. Cholinesterase inhibition against acetyl- (AChE) and butyryl cholinesterase (BChE) was measured by the spectrophotometric method at concentrations of 25, 50, and 100 microg/ml. Results revealed that the n-hexane and acetone extracts exerted a notable inhibition against both AChE (62.9 ±0.9% and 50.8 ±2.1%, respectively) and BChE (76.9 ± 2.2% and 45.6 ± 1.3%) respectively [49-50],

2.19. *Ficus religiosa*

The effect of flavonoid-rich ethyl acetate fraction of the crude extract of *Ficus religiosa* in combined with phenytoin was evaluated on seizure severity, depressive behavior, and cognitive deficit in pentyleneetetrazol (PTZ)-kindled mice. Combined treatment of flavonoid-rich ethyl acetate fraction (2.5, 5, and 10 mg/kg; ip) with a sub-effective dose of phenytoin (15 mg/kg; ip) in post kindled animals once daily for fifteen days showed a dose-dependent decrease in the seizure severity score, a decreased number of mistakes, increased step-down latency in passive shock avoidance paradigm, and decreased immobility time in the tail suspension test in comparison with the phenytoin only-treated
group. Biochemical investigations of the brain tissue showed amelioration of thiobarbituric acid reactive substances, reduced glutathione levels, and reduced catalase and acetyl cholinesterase activities.

2.20. Foeniculum vulgare

The nootropic and anti-cholinesterase potential of *Foeniculum vulgare* was studied in mice. Methanolic extract of the whole plant of *Foeniculum vulgare* administered for eight successive days ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging- induced memory deficits in mice. The passive avoidance paradigm was used as an exoceptive behavioral model for assessing memory. *Foeniculum vulgare* extract increased step-down latency and acetyl cholinesterase inhibition in mice significantly. The authors postulated that *Foeniculum vulgare* can be employed in treatment of cognitive disorders such as dementia and Alzheimer's disease.

2.21. Fritillaria imperialis

The steroidal bases (impericine, forticine, delavine, persicanidine A, and imperialine) isolated from the ethanol extract of the air-fried bulbs of *Fritillaria imperialis* possessed inhibitory effect on compounds causing anti-acetyl cholinesterase and anti-butyryl cholinesterase activity.

In order to check the structure-activity relationship and prepare more potent derivatives of imperialine with anti-cholinergic activity, imperialinol, 3 beta-acetoxyimperialine, 3 beta-propionoxyimperialine, and 3 beta-butyroxyimperialine were prepared. 3 beta propionoxyimperialine, and 3 beta-butyroxyimperialine displayed better anticholinergic activity against muscarinic receptors of the heart and brain than imperialine. The decrease in activity in imperialinol showed the importance of the 6-keto functionality in imparting the anti-cholinergic activity.

2.22. Fumaria officinalis

Isoquinoline alkaloids isolated from aerial parts of *Fumaria officinalis* were evaluated for their acetyl-cholinesterase, butyryl-cholinesterase, prolyl oligo peptidase (POP), and glycogen synthase kinase-3β inhibitory activities. Parfumidine and sinactine exhibited potent POP inhibitory activities (IC50 99±5 and 53±2 μM, respectively). *Fumaria officinalis* appeared the most potent acetyl cholinesterase inhibitors among many *Fumaria* species, on a plant dry weight basis (IC50 = 4.7 ±0.2 mg dry weight/ ml). However, acetyl-cholinesterase inhibitory effects were correlated to the amount of protopine contained in 1 g of complex alkaloid isolated from the species.

2.23. Fumaria parviflora

The chloroform: methanol (1:1) extracts of a number of the plant species belonging to eight families, including *Fumaria parviflora*, were screened for their anti-cholinesterase activity on acetyl-cholinesterase (AChE) and butyryl-cholinesterase (BChE) enzymes by in vitro at 10 microg/ml and 1 mg/ml concentrations. Among the screened extracts, all of the Fumaria extracts displayed highly potent inhibition against both of the enzymes at 1 mg/ml concentration compared to the standard.

2.24. Galium verum

With the applying of modified Ellman's method, *Galium verum* methanol extracts showed slight activation of human serum cholinesterase (16.28 ± 0.09 %).

2.25. Geum urbanum

The extracts from three Romanian medicinal plants (*E. planum, Geum urbanum*, and *C. benedictus*) were investigated for their possible neuro-protective potential. The in vitro neuroprotective activity of the extracts were investigated via inhibition of acetyl cholinesterase. AChE inhibitory activities of *Geum urbanum* aqueous extract were 27.03±1.5, 36.48±1.7 and 79.11±3.9 % at concentration of 0.75 mg/ml, 1.5 mg/ml and 3 mg/ml respectively and IC50 mg/ml was 2.293±0.14, while AChE inhibitory activities of *Geum urbanum* ethanol extract were 54.74±2.7, 73.53±5.1 and 86.77±5.1 respectively and IC50 mg/ml was 0.51±0.03.

2.26. Glaucium corniculatum

The chloroform: methanol (1:1) extracts of a number of the plant species included *Glaucium corniculatum* were screened for their anti-cholinesterase activity. The extracts of *Glaucium corniculatum* showed remarkable inhibitory activity 86.55± 0.67% at concentration of 1mg/ml.
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2.27. *Glycyrrhiza glabra*

The effect of glabridin isolated from the roots of *Glycyrrhiza glabra* was investigated on cognitive functions and cholinesterase activity in mice. Glabridin (1, 2 and 4 mg/kg, po) was administered daily for 3 successive days to mice. The higher doses (2 and 4 mg/kg po) of glabridin significantly antagonized the amnesia induced by scopolamine (0.5mg/kg ip) in both the elevated plus maze test and passive avoidance test. Glabridin (2 and 4 mg/kg po) also remarkably reduced the brain cholinesterase activity in mice compared to the control group.\(^{68-69}\)

2.28. *Gossypium herbaceam*

The acetyl-cholinesterase (AChE) inhibition activity of a standardized extract from the flowers of the *Gossypium herbaceam* (GHE) were investigated using in vitro assays. The results revealed that GHE exhibited activity against AChE and possessed efficient free radical scavenging activity, which may be helpful in preventing or alleviating patients suffering from Alzheimer's disease.\(^{70-71}\)

2.29. *Haplophyllum tuberculatum*

The oil showed weak acetyl-cholinesterase (AChE) inhibitory activity, compared to standard substances, whereas no inhibition on butyryl-cholinesterase (BuChE) activity was observed. \(^{72}\) *Haplophyllum tuberculatum* was studied for AChE inhibitory activity. The inhibitory activity of acetyl cholinesterase was mainly accumulated in the chloroform and ethyl acetate fractions of different parts extracts of *Haplophyllum tuberculatum*. The most active was the stem ethyl acetate fraction with an inhibitory effect of 79% and IC\(_{50}\) of 0.45 μg/ml. Other fractions possessed an inhibitory effect at arrange between 70 – 77%. \(^{73-74}\)

2.30. *Hibiscus rosa-sinensis*

An aqueous extract of *Hibiscus rosa-sinensis* showed 62.02%±0.03 inhibitory activity against AChE and 57.83%±0.05 inhibitory activity against BuChE enzymes. Accordingly, *Hibiscus rosa-sinensis* could be useful in improving memory and other cognitive function associated with the cholinergic system.\(^{75-76}\)

2.31. *Hibiscus sabdariffa*

*Hibiscus sabdariffa* (100 and 200 mg/kg, po) significantly attenuated amnestic deficits induced by scopolamine (0.4 mg/kg, ip) and natural aging. *Hibiscus sabdariffa* (100 and 200 mg/kg) decreased the transfer latencies and increased step down latencies significantly in the aged mice and scopolamine induced amnesic mice as compared with piracetam (200 mg/kg, ip). Acetyl-cholinesterase activity in the whole brain was significantly decreased in mice which could be refer to the underlying mechanism of action.\(^{77-78}\)

2.32. *Inula graveolens*

*Inula graveolens* essential oil possessed AChE inhibitory activity.\(^{79-80}\)

2.33. *Juglans regia*

Extracts of *Juglans regia* fruits and leaves exhibited low inhibition of butyryl-cholinesterase, and it possessed no significant effect on acetyl cholinesterase.\(^{81-82}\)

2.34. *Lawsonia inermis*

In studying the anti-cholinesterase activity of hexane, chloroform and methanolic extracts of henna seeds, the methanol extract inhibited a potent anti-cholinesterase activity (IC\(_{50}\) =66.6 mg/l), while, chloroform and hexane extracts exerted no anti-cholinesterase activity (IC\(_{50}\)>100 mg/l).\(^{83-84}\)

2.35. *Leontice leontopetalum*

Lupanine, a quinolizidine alkaloid isolated from the tubers of *Leontice leontopetalum* subsp. ewersmannii, showed almost the same butyryl-cholinesterase inhibitory activity with galantamine at 200 μg/ml. \(^{85-86}\)

2.36. *Malva neglecta*

Extracts (methanol, petroleum ether and acetone) of *Malva neglecta* (whole plants in flowering stage) showed moderate activity against acetyl-and butyryl-cholinesterase enzymes. Methanol extract exerted the highest activity among all the tested extracts against acetyl-and butyryl-cholinesterase enzymes. At 200 μg/ml methanol extract possessed (53.68
and 63.95% inhibition), acetone extract (38.65±1.39 and 57.69±0.63% inhibition) and petroleum ether extract showed (30.13±1.32 and 43.68±1.12 % inhibition) against acetyl- and butyryl- cholinesterase enzymes respectively (87-88).

2.37. Matricaria chamomilla

The scopolamine-induced alteration of the acetyl-cholinesterase activity and the oxidant- antioxidant balance in the rat hippocampus was recovered by the treatment with *Matricaria chamomilla* extract. The extract also restored the scopolamine-decreased BDNF expression and increased IL1β expression in the rat hippocampus (89).

2.38. Melia azedarach

Aqueous, potassium phosphate buffer (pH 7.2), hydro-ethanolic solution 70:30 and hydro-ethanolic solution 50:50. Extracts of *Melia azedarach* leaves were investigated for the inhibitory effect on butyrylcholinesterase activity in homogenates rat livers. The introduction of *Melia azedarach* extracts in the reaction mixture produced a variety of inhibitions (> 45 to 100%), independent on its concentration (0.5 to 2.0 mg/ml) and extract type (90).

2.39. Melissa officinalis

*Melissa officinalis* decreased acetyl-cholinesterase mRNA level by 52% in the cortex and caused a strong significant inhibition of beta-secretase 1 mRNA transcription (64% in the frontal cortex; 50% in the hippocampus). However, the extract produced insignificant inhibition of acetyl-cholinesterase activity in the frontal cortex (91).

The extract of *Melissa officinalis* was capable of inhibiting the acetyl-cholinesterase enzyme, in a time and dose-dependent manner. Activity of the extract at 10 min was estimated as 1.72±0.16 microm equivalents of physostigmine/mg of the extract. The contents of the most potent fraction were identified as cis- and trans-rosmarinic acid isomers and a rosmarinic acid (92).

2.40. Mentha longifolia

A remarkable acetyl-cholinesterase inhibitory activity of the ethyl acetate fraction of *Mentha longifolia* (IC₅₀=12.3μg/ml) and essential oils suggested their neuroprotective property against Alzheimer’s disease (93). Pulegone the main constituent (32.3%) of the essential oil possessed strong butyryl-cholinesterase inhibitory activity (77.36 ± 0.29%) (94).

2.41. Myrtus communis

The dichloromethane, acetone, ethyl acetate and methanol extracts (200 μg/ml) of the leaves and berries of *Myrtus communis* were screened against acetyl-cholinesterase, butyryl-cholinesterase and tyrosinase, the enzymes linked to neurodegenerative diseases. The extracts showed a moderate acetyl-cholinesterase (17.49 ± 3.99% to 43.15 ± 1.55%) and tyrosinase inhibition (4.48 ± 1.50% to 40.53 ± 0.47%). The leaf extracts were ineffective against butyryl-cholinesterase, while the berry extracts displayed inhibition between 21.83 ± 3.82% and 36.80 ± 2.00% (95).

2.42. Narcissus tazetta

Amaryllidaceae alkaloids and Narcissus extracts were used in Alzheimer’s disease as inhibitors of acetylcholine esterase. Alkaloids, belonging to the galanthamine and lycorine skeleton types, exhibited the more potent acetylcholine esterase inhibitory effects (96).

The *in vitro* anti-acetylcholinesterase (AChE) assay results indicated that the extracts of the bulbs of *Narcissus tazetta* were effective inhibitors for AChE enzyme (100% inhibition at a concentration of 1000 μg/ml, 87.13% at a concentration of 100 μg/ml and 58.23% at a concentration of 10μg/ml). The aerial parts also showed noticeable inhibition on AChE (100% inhibition at a concentration of 1000μg/ml, 67.47 % at a concentration of 100 μg/ml and 30.59% at a concentration of 10μg/ml). Both samples also inhibited butyryl cholinesterase (BuChE), the bulbs of the plant caused (85.23 % inhibition at a concentration of 1000 μg/ml, 37.96% at a concentration of 100 μg/ml and 23.90 % at a concentration of 10μg/ml), while the aerial parts caused (92.67 % inhibition at a concentration of 1000 μg/ml, 35.06 % at a concentration of 100 μg/ml and 11.02 % at a concentration of 10μg/ml) (97).

The alkaloids (lycorine, tazettine, N-nor-galanthamine, haemanthamine) and 3-epi-hydroxybulbispermine isolated from *N. tazetta* subsp. *tazetta* were investigated for acetyl-cholinesterase inhibiting activity at 10 μg/ml concentration. The acetyl-cholinesterase inhibiting rates were: lycorine 43.69%, tazettine 36.34%, galanthamine 48.00%, 3-epihydroxybulbispermine 30.18% N-nor-galanthamine 34.09% and haemanthamine 20.8 %. Chloroform: methanol extract and crude alkaloid extract of the plant were also possessed acetyl-cholinesterase inhibiting activity (46.62±0.77 and 46.96±0.08% respectively) (98-99).
2.43. *Nigella sativa*

*Nigella sativa* methanol, n-hexane, and aqueous seed extracts were tested for their inhibitory activity against butyrylcholinesterase (BChE). All extracts showed inhibitory activity against BChE, with methanol seed extract possessed the highest inhibitory activity IC50 of 79.11 ± 6.06 μg/ml\(^{108-109}\).

2.44. *Peganum harmala*

*Peganum harmala* methanol extract showed irreversible inhibitory effect on acetylcholinesterase (AChE) at IC50 68 μg/ml\(^{102}\). The acetylcholinesterase (AChE) inhibitory activities of extract, alkaloid fraction and flavonoid fraction of *Peganum harmala* were evaluated in normal male mice. The anti-amnesic effects were measured in scopolamine-induced memory deficits mice by the Morris water maze tasks. The AChE activity was significantly decreased and the content of acetylcholine (ACh) was significantly increased in normal mice cortex and hippocampus by treatment with the extract at dose of 183, 550, 1650mg/kg and alkaloid fraction at dose of 10, 30, 90 mg/kg. In the Morris water maze tasks, scopolamine decreased both the swimming time within the target zone and the number of crossings where the platform had been placed, were significantly reversed by treatment with extract at dose of 550, 1650mg/kg and alkaloid fraction at dose of 30, 90mg/kg. The activity and protein expression of AChE was significantly decreased and the content of ACh was significantly increased in cerebral cortex of scopolamine-induced mice by treatment with extract at dose of 183, 550, 1650mg/kg and alkaloid fraction at dose of 10, 30, 90mg/kg\(^{103}\).

2.45. *Pimpinella anisum*

Ethanolic extract from the fruits of *Pimpinella anisum* showed anti- AChE and anti- BChE activity, with IC50 values of 227.5 and 362.1 microg/ml, respectively. The abundant constituents of the extract (trans-anethole) exhibited the highest activity against AChE and BChE with IC50 values of 134.7 and 209.6 microg/ml, respectively\(^{104}\).

2.46. *Portulaca oleracea*

Three compounds isolated from *Portulaca oleracea* possessed anti-cholinesterase activities\(^{105}\). Oleraisoindole A, obtained from the extract of the *Portulaca oleracea* possessed anti-cholinesterase effect with IC50 value of 60.4 μM\(^{106}\). Oleraindole A and oleraindole B isolated from the aqueous extract of *Portulaca oleracea* exhibited relatively high anti-cholinesterase activity with IC50 values of 55.12 ± 0.20 μM and 46.76 ± 0.08 μM respectively\(^{107-108}\).

2.47. *Potentilla reptans*

The ethyl acetate, methanol and water extract of the aerial parts of *Potentilla reptans* possessed enzyme inhibitory activities. Their acetyl-cholinesterase inhibitory activities were 3.99 ± 0.08, 3.56 ± 0.22, 1.30 ± 0.22 mg galantamine equivalents /g extract\(^{109}\).

2.48. *Prunus armeniaca*

The anti-cholinesterase activity of sweet and bitter extracts of apricot kernels was examined in vitro. The neuroprotective effect of aqueous extracts and amygdalin was also investigated against H2O2-induced cell death in PC12 neurons. Among them, the best acetyl-cholinesterase (AChE) inhibitory activity (IC50 = 134.93 ± 2.88 μg/ml) and neuroprotectivity (p< 0.0001) were exerted by the aqueous extract of bitter type\(^{110}\).

The polyphenol-rich apricot leaf extract was screening for anti-cholinesterase (AChE and BChE) activity. The activity of the extract was low, less than 10%, but significantly proportional to the polyphenol concentration of evaluated cultivars\(^{111}\).

2.49. *Prunus mahaleb*

The anti-cholinesterase activity of the methanol and hexane extracts of *Prunus mahaleb* seeds was evaluated in vitro. Both extracts inhibited the AChE and BChE. The methanolic extract showed more potent anti-cholinesterase activity than hexane extract\(^{112}\).

2.50. *Prunus persica*

The acetyl-cholinesterase inhibitory effects of orally administered *Prunus persica* extracts were examined on the cholinesterase activity in the brain and plasma of rats. After the sequential solvent fractionation of the methanol extract of *Prunus persica*, the highest inhibitory effect was caused by chloroform fraction (75%, with IC50 value of 5.6 microg/ml). Oral administration of water extract or tacrine caused a dose-dependent inhibition of brain and plasma cholinesterase activities. The ID50 values of these compounds for brain cholinesterase activity were 2.7 g/kg and 8.9
mg/kg, respectively. On the other hand, the ID<sub>50</sub> values for plasma cholinesterase activity were 18.6 g/kg and 27.5 mg/kg, respectively. The ratios of the ID<sub>50</sub> (plasma < brain) were 6.0 and 3.1, respectively. These results suggest that orally administered <i>Prunus persica</i> extract penetrated into the brain and inhibited cholinesterase there and that the extract was potent inhibitor of brain cholinesterase in comparison with plasma cholinesterase <i>in vivo</i>.[113]

2.51. <i>Pulicaria dysenterica</i>

The anti-cholinesterase activities of the petroleum ether, acetone, and methanol and water extracts of <i>Pulicaria dysenterica</i> were investigated using Ellman method. The petroleum ether extract exhibited high inhibition (65.33%), while the acetone, methanol and water extracts possessed moderate activity against acetyl-cholinesterase enzyme at 200 pg/ml. None of the extracts was found to be active against butyryl-cholinesterase.[114]

3. Conclusion

AChE and BChE inhibitors are neurotoxic compounds capable of causing central, peripheral or both central and peripheral cholinergic crises. A number of these compounds are widely used for the symptomatic treatment of Alzheimer’s disease, other dementias and myasthenia gravis. Many of these inhibitors interact with the second known cholinesterase, butyryl cholinesterase (BChE). The current review discussed the medicinal plants with cholinesterase inhibitory effects to encourage their uses for many medical purposes.

Compliance with ethical standards

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