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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 LC_{50}) 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 *Lymnaea 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 decreasedthe 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 IC_{50} 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 orallywas 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) was10.90 ±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 fornew 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. Accordigly, *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 IC_{50} 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. *horizantalis* (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-acethyl cholinesterasestudyof *Cupressus sempervirens* essential oil was investigated. It showed that essential oil inhibitory concentration (IC_{50}) 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 (IC_{50} = 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 (IC_{50} =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 givenas 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 carot*a

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 pentylenetetrazol (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 [51-52].

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 exteroceptive 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 [53-54].

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 [55].

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 [56-57].

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) [58]. *Fumaria officinalis* appeared the most potent acetyl cholinesterase inhibitors among many *Fumaria* species, on a plant dry weight basis (IC_{50} = 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 [59-60].

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 [61-62].

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 %) [63-64].

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 IC_{50} 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 0.513±0.03 [65-66].

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 [67].

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 cholinestrase was mainly accumulated in the chloforom 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 (IC50>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 microg 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* (IC_{50}=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 butyryl-cholinesterase (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 [100-101].

2.44. *Peganum harmala*

Peganum harmala methanol extract showed irreversible inhibitory effect on acetyl-cholinesterase (AChE) at IC_{50}: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 IC_{50} 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 IC_{50} 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 IC_{50} value of 60.4 µM [106]. Oleraindole A and oleraindole B isolated from the aqueous extract of *Portulaca oleracea* exhibited a relatively high anti-cholinesterase activity with IC_{50} 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 H_2O_2-induced cell death in PC12 neurons. Among them, the best acetyl-cholinesterase (AChE) inhibitory activity (IC_{50} = 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%, withIC_{50} 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 ID_{50} 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_{50} values for plasma cholinesterase activity were 18.6 g/kg and 27.5 mg/kg, respectively. The ratios of the ID_{50} (plasma < brain) were 6.0 and 3.1, respectively. These results suggest that orally administered *Prunus persica* extract penetrated into the brain and inhibited cholinesterase there and that the extract was potent inhibitor of brain cholinesterase in comparison with plasma cholinesterase *in vivo* [113].

2.51. *Pulicaria dysenterica*

The anti-cholinesterase activities of the petroleum ether, acetone, and methanol and water extracts of *Pulicaria dysenterica* 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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References

[1] Massoulie J, Pezzementi L, Bon S, Krejci E, Vallette FM. Molecular and cellular biology of cholinesterases. ProgNeurobiol 1993; 41(1): 31-91.

[2] Colovic MB, Krstic DZ, Lazarevic-Pacti TD, Bondcic AM and Vasic VM. Acetylcholinesterase inhibitors: Pharmacology and toxicology. Current Neuropharmacology 2013; 11: 315-335.

[3] Huang YJ, Huang Y, Baldassarre H, Wang B, Lazaris A, Leduc M, Bilodeau AS. Recombinant human butyrylcholinesterase from milk of transgenic animals to protect against organophosphate poisoning. ProcNatlAcadSci USA 2007; 104(34): 13603- 13608.

[4] Al-Snafi AE. Medicinal plants possessed anti-Parkinsonian effects with emphasis on their mechanisms of action. GSC Biological and Pharmaceutical Sciences 2021; 17(1): 232–237.

[5] Al-Snafi AE. Medicinal plants possessed beneficial therapeutic effects in Alzheimer's disease and memory deficits. GSC Biological and Pharmaceutical Sciences 2021; 17(2): 8–33.

[6] Al-Snafi AE. Medicinal Plants with neuroprotective effects. GSC Biological and Pharmaceutical Sciences 2021; 17(1): 213–231.

[7] Al-Snafi AE. Therapeutic properties of medicinal plants: a review of medicinal plants with central nervous effects (part 1). Int J of Pharmacology & Toxicology 2015; 5(3): 177-192.

[8] Al-Snafi AE. Medicinal plants with central nervous effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(8): 52-75.

[9] Costa Marques TH, Santos De Melo CH, Fonseca De Carvalho RB, Costa LM, De Souza AA, David JM, De Lima David JP and De Freitas RM. Phytochemical profile and qualification of biological activity of an isolated fraction of *Bellis perennis*. Biol Res 2013; 46(3): 231-238.

[10] Al-Snafi AE. The Pharmacological importance of *Bellis perennis* - Areview. International Journal of Phytotherapy 2015; 5(2): 63-69.

[11] Tripathi SM, Singh VK, Singh S and Singh DK. Enzyme inhibition by the molluscicidal agent *Punicagranatum* Linn. Bark and *Canna indica* Linn root. Phytotherapy Research 2004; 18(7): 501-506.

[12] Al-Snafi AE. Bioactive componentsand pharmacological effects of *Canna indica*- An overview. International Journal of Pharmacology and Toxicology 2015; 5(2): 71-75.

[13] Grosso C, Vinholes J,Silva L R, de Pinho B G, Gonçalves R F, Valentão P,Jäger A K andAndrade P B. Chemical composition and biological screening of *Capsella bursa-pastoris.* Brazilian Journal of Pharmacognosy 2011; 21(4): 635-644.

[14] Al-Snafi AE. The chemical constituents and pharmacological effects of *Capsella bursa-pastoris* - A review. International Journal of Pharmacology and Toxicology 2015; 5(2): 76-81.

[15] Ahmed N. Alloxan diabetes-induced oxidative stress and impairment of oxidative defense system in rat brain: neuroprotective effects of *Cichorium intybus*. Int J Diabetes & Metabolism 2009; 17: 105-109.

[16] Al-Snafi AE. Medical importance of *Cichorium intybus* – A review. IOSR Journal of Pharmacy 2016; 6(3): 41-56.

[17] Wu CR, Lin HC and Su MH. Reversal by aqueous extracts of *Cistanche tubulosa* from behavioral deficits in Alzheimer's disease- likerat model: relevance foramyloid deposition and central neurotransmitter function. BMC Complement Altern Med 2014; 14: 202-212.

[18] Al-Snafi AE. Bioactive metabolites and pharmacology of *Cistanche tubulosa*- A review. IOSR Journal of Pharmacy 2020; 10(1): 37-46.

[19] Menichini F. Evaluation of *Citrus aurantifolia* peel and leaves extracts for their chemical composition, antioxidant and anti-cholinesterase activities. J Sci Food Agric 2002; 92: 2960–2967.

[20] Al-Snafi AE. Nutritional value and pharmacological importance of citrus species grown in Iraq. IOSR Journal of Pharmacy 2016; 6(8): 76-108.

[21] Taranalli AD and Cheeramkuzhy TC. Influence of *Clitoria ternatea* extracts on memory and central cholinergic activity in rats. Pharm Biol 2000; 38(1): 51-56.

[22] Al-Snafi AE. Pharmacological importance of *Clitoria ternatea*– A review. IOSR Journal of Pharmacy 2016; 6(3): 68-83.

[23] Sevim D, Senol FS, Budakoglu E, Orhan IE, Bilge S and Kaya E. Studies on anticholinesterase and antioxidant effects of samples from *Colchicum* L. genus of Turkish origin. Fabad J Pharm. Sci2010; 35: 195-201.

[24] Dhivya PS, Sobiya M, Selvamani P and Latha S. An approach to Alzheimer's disease treatment with cholinesterase inhibitory activity from various plant species. International Journal of PharmTech Research 2014; 6(5): 1450-1467.

[25] Chattipakorn S, Pongpanparadorn A, Pratchayasakul W, Pongchaidacha A, Ingkaninan K and Chattipakorn N. Tabernaemontanadivaricata extract inhibits neuronal acetylcholinesterase activity in rats. J Ethnopharmacol 2007; 110: 61–68.

[26] Al-Snafi AE. Medicinal importance of *Colchicum candidum*- A review. The Pharmaceutical and Chemical Journal 2016; 3(2): 111-117.

[27] Mani V, Parle M, Ramasamy K and Abdul Majeed AB. Reversal of memory deficits by *Coriandrum sativum* leaves in mice. J Sci Food Agric 2011; 91(1): 186-192.

[28] Mani V andParle M. Memory- enhancing activity of *Coriandrum sativum* in rats. Pharmacology Online 2009; 2: 827-839.

[29] Al-Snafi AE. A review on chemical constituents and pharmacological activities of *Coriandrum sativum*. IOSR Journal of Pharmacy 2016; 6(7): 17-42.

[30] Khare P,Yadav G, Chaudhary S andSingh L. Investigation on protective effects of *Cressacretica* extract in scopolamine- induced memory impairment. International Journal of Pharmacology and Toxicology 2014; 2(1): 13-16.

[31] Khare P, Yadav G, Chaudhary S, Singh L, Yadav G and Verma S. Evaluation of nootropic activity of *Cressa cretica* in scopolamine- induced memory impairment in mice. International Journal of Pharmacology and Toxicology 2014; 2 (2): 24-29.

[32] Al-Snafi AE. The chemical constituents and therapeutic importance of *Cressa cretica*- A review. IOSR Journal of Pharmacy 2016; 6(6): 39-46.

[33] Geromichalos GD, Lamari FN, Papandreou MA, Trafalis DT, Margarity M, Papageorgiou A andSinakos Z. Saffron as a source of novel acetylcholinesterase inhibitors: molecular docking and *in vitro* enzymatic studies. J Agric Food Chem 2012; 60(24): 6131-6138.

[34] Al-Snafi AE. The pharmacology of *Crocus sativus*- A review. IOSR Journal of Pharmacy 2016; 6(6): 8-38.

[35] Tumen I, Senol FS and Orhan IE. Evaluation of possible *in vitro* neurobiological effects of two varieties of *Cupressus sempervirens* (Mediterranean cypress) through their antioxidant and enzyme inhibition actions. Türk Biyokimya Dergisi (Turk J Biochem) 2012; 37 (1): 5-13.

[36] Aazza S, Lyoussi B and Miguel MG. Antioxidant and antiacetylcholinesterase activities of some commercial essential oils and their major compounds. Molecules 2011; 16: 7672-7690.

[37] Al-Snafi AE. Medical importance of *Cupressus sempervirens*- A review. IOSR Journal of Pharmacy 2016; 6(6): 66-76.

[38] Khadri A, Serralheiro MLM, Nogueira JMF, Smiti A and Araujo MEM. Antioxidant and antiacetylcholinesterase activities of essential oils from *Cymbopogon schoenanthus* L Spreng. Determination of chemical composition by GC–mass spectrometry and 13C NMR. Food Chemistry 2008; 109(3): 630-637.

[39] Khadri A,Neffati M,Smiti S,Falé P, Rosa A, Lino L, Luisa M, Serralheiro M, Eduarda M andAraújo M.Antioxidant, antiacetylcholinesterase and antimicrobial activities of *Cymbopogon schoenanthus* L. Spreng (lemon grass) from Tunisia. LWT - Food Science and Technology 2010; 43(2): 331-336.

[40] Al-Snafi AE. The chemical constituents and pharmacological activities of *Cymbopagon schoenanthus*: A review. Chemistry Research Journal 2016; 1(5): 53-61.

[41] Sau S and Handral M. Evaluation of memory enhancing activity of leaf extract of *Dalbergia sissoo* in mice. International Journal of Pharmaceutical Sciences and Drug Research 2015; 7(3): 263-269.

[42] Al-Snafi AE. Chemical constituents and pharmacological effects of *Dalbergia sissoo* - A review. IOSR Journal of Pharmacy 2017; 7(2): 59-71.

[43] Krenzelok EP. Aspects of datura poisoning and treatment. Clin Toxicol (Phila) 2010; 48(2): 104-110.

[44] Al-Snafi AE. Medical importance of *Datura fastuosa* (syn: *Datura metel*) and *Datura stramonium* - A review. IOSR Journal of Pharmacy 2017; 7(2): 43-58.

[45] Vasudevan M and Parle M. Pharmacological evidence for the potential of *Daucus carota* in the management of cognitive dysfunctions. Biol Pharm Bull2006; 29(6): 1154-1161.

[46] Al-Snafi AE. Nutritional and therapeutic importance of *Daucus carota*- A review. IOSR Journal of Pharmacy 2017; 7(2): 72-88.

[47] Cahlíková L, Macáková K, Kunes J, Kurfürst M, Opletal L, Cvacka J, Chlebek J and Blundene G. Acetylcholinesterase and butyrylcholinesterase inhibitory compounds from *Eschscholzia californica* (Papaveraceae). Nat Prod Commun 2010l; 5(7): 1035-1038.

[48] Al-Snafi AE. *Eschscholzia californica*: A phytochemical and pharmacological review. Indo Am J P Sci 2017; 4(02): 257-263.

[49] Orhan IE, Ustün O and Sener B. Estimation of cholinesterase inhibitory and antioxidant effects of the leaf extracts of Anatolian *Ficus carica* var. *domestica* and their total phenol and flavonoid contents. Nat Prod Commun 2011; 6(3): 375-378.

[50] Al-Snafi AE. Nutritional and pharmacological importance of *Ficus carica* - A review. IOSR Journal of Pharmacy 2017; 7(3): 33-48.

[51] Singh P, Singh D and Goel RK. *Ficus religiosa* L. figs - a potential herbal adjuvant to phenytoin for improved management of epilepsy and associated behavioral comorbidities. Epilepsy Behav 2014; 41: 171-178.

[52] Al-Snafi AE. Pharmacology of *Ficus religiosa*- A review. IOSR Journal of Pharmacy 2017; 7(3): 49-60.

[53] Joshi H and Parle M. Cholinergic basis of memory-strengthening effect of *Foeniculum vulgare* Linn. Journal of Medicinal Food 2006, 9(3): 413-417.

[54] Al-Snafi AE. The chemical constituents and pharmacological effects of *Foeniculum vulgare* - A review. IOSR Journal of Pharmacy 2018; 8(5): 81-96.

[55] Masterova I, Kettmann V, Majer J and Tomko J. Isobaimonidine a new alkaloid from *Fritillaria imperialis*. Archiv der Pharmazie (Weinheim) 1982; 315(2): 157-164.

[56] Gilani AH, Shaheen F, Christopoulos A and Mitchelson F. Interaction of ebeinone, an alkaloid from *Fritillaria imperialis*, at two muscarinic acetylcholine receptor subtypes. Life Sci 1997; 60(8): 535-544.

[57] Al-Snafi AE. *Fritillaria imperialis*- A review. IOSR Journal of pharmacy 2019; 9(3): 47-51.

[58] Chlebek J, Novák Z, Kassemová D, Šafratová M, Kostelník J, Malý L, Ločárek M, Opletal L, Hošt'álková A, Hrabinová M, Kuneš J, Novotná P, Urbanová M, Nováková L, Macáková K, Hulcová D, Solich P, Pérez Martín C, Jun D and Cahlíková L. Isoquinoline alkaloids from *Fumaria officinalis* L. and their biological activities related to Alzheimer's disease. Chem Biodivers 2016; 13(1): 91-99.

[59] Vrancheva RZ, Ivanov IG, Aneva IY, Dincheva IN, Badjakov IK and Pavlov AI. Alkaloid profiles and acetylcholinesterase inhibitory activities of *Fumaria* species from Bulgaria. Z Naturforsch 2016; aop: 1-6.

[60] Al-Snafi AE. Constituents and pharmacology of *Fumaria officinalis*- A review. IOSR Journal of Pharmacy 2020; 10(1): 17-25.

[61] Orhan I, Sener B, Choudhary MI and Khalid A. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of some Turkish medicinal plants. J Ethnopharmacol 2004; 91(1): 57- 60.

[62] Al-Snafi AE. *Fumaria parviflora*- A review. Indo Am J P Sc 2018; 5(3): 1728-1738.

[63] Mitic VD, Stankov-Jovanovic VP, Ilic MD, Vasiljevic PJ, Zabar AL and Stojanovic GS. The antioxidant, hemolytic and cholinesterase inhibition properties of *Galiumverum*L. and *Tragopogon pratensis* subsp. *pratensis.* Bulgarian Chem Commun 2014; 46(2): 269-276.

[64] Al-Snafi AE. *Galium verum* -A review. Indo Am J P Sc 2018; 5 (4): 2142-2149.

[65] Paun G, Neagu E, Albu C and Radu GL. Inhibitory potential of some Romanian medicinal plants against enzymes linked to neurodegenerative diseases and their antioxidant activity. Pharmacogn Mag 2015; 11(Suppl 1): S110-116.

[66] Al-Snafi AE. Constituents and pharmacology of *Geum urbanum*- A review. IOSR Journal of pharmacy 2019; 9(5): 28-33.

[67] Orhan I, Sener B, Choudhary MI and Khalid A. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of some Turkish medicinal plants. J Ethnopharmacol 2004; 91: 57–60.

[68] Cui YM, Ao MZ, Li W and Yu LJ. Effect of glabridin from *Glycyrrhiza glabra* on learning and memory in mice. Planta Med 2008; 74(4): 377-380.

[69] Al-Snafi AE. *Glycyrrhiza glabra*: A phytochemical and pharmacological review. IOSR Journal of Pharmacy 2018; 8(6): 1-17.

[70] Zhao Y, Dou J, Wu T and Aisa H. Investigating the antioxidant and acetylcholinesterase inhibition activities of *Gossypium herbaceam*. Molecules 2013; 18(1): 951-962.

[71] Al-Snafi AE. Chemical constituents and pharmacological activities of *Gossypium herbaceum* and *Gossypium hirsutum* - A review. IOSR Journal of Pharmacy 2018; 8(5): 64-80.

[72] Al-Rehaily AJ, Alqasoumi SI, Yusufoglu HS, Al-Yahya MA, Demirci B, Tabanca N, Wedge DE, Demirci F, Bernier UR, Becnel JJ, Temel HE and Can Baser KH. Chemical composition and biological activity of *Haplophyllum tuberculatum* Juss essential oil. Journal of Essential Oil Bearing Plants 2014; 17(3): 452-459.

[73] Ibrahim NS, El. Said AG, Mohamed YA and Ali HA. *In vitro* inhibition of acetyl cholinestrase by *Haplophyllum tuberculatum* extracts. The Sixth Annual Post-graduate Studies & Scientific Research Conference 2015: 152, http: //khartoumspace. uofk.edu/handle/123456789/19525

[74] Al-Snafi AE. Pharmacological importance of *Haplophyllum* species grown in Iraq- A review. IOSR Journal of Pharmacy 2018; 8(5): 54-62.

[75] Nazool M and Kumar S. Dual inhibition of cholinesterase enzyme by an aqueous extract of *Hibiscus rosa-sinensis* L. International Journal of Pharma Research & Review 2015; 4(5): 6-10.

[76] Al-Snafi AE. Chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis*- A review. IOSR Journal of Pharmacy 2018; 8 (7): 101-119.

[77] Hanumanthachar J and Parle M. Nootropic activity of calyces of *Hibiscus sabdariffa* Linn. IJPT 2006; 5(1): 15-20.

[78] Al-Snafi AE. Pharmacological and therapeutic importance of *Hibiscus sabdariffa*- A review. International Journal of Pharmaceutical Research 2018; 10(3): 451-475.

[79] Dohi S, Terasaki M and Makino M. Acetylcholinesterase inhibitory activity and chemical composition of commercial essential oils. J Agric Food Chem 2009; 57(10): 4313-4318.

[80] Al-Snafi AE. Chemical constituents and pharmacological effect of *Inula graveolens* (Syn: *Dittrichia graveolens*)- A review. Indo Am J P Sc 2018; 5 (4): 2183-2190.

[81] Orhan IE, Suntar IP and Akkol EK. *In vitro* neuroprotective effects of the leaf and fruit extracts of *Juglans regia* L. (walnut) through enzymes linked to Alzheimer's disease and antioxidant activity. Int J Food Sci Nutr 2011; 62(8): 781-786.

[82] Al-Snafi AE. Chemical constituents, nutritional, pharmacological and therapeutic importance of *Juglans regia*- A review. IOSR Journal of Pharmacy 2018; 8(11): 1-21.

[83] Chaibi R, Drine S and Ferchichi A. Chemical study and biological activities of various extracts from *Lawsoniainermis*(Henna) seeds. Acta Medica Mediterranea 2017; 33: 981-986.

[84] Al-Snafi AE. A review on *Lawsonia inermis*: A potential medicinal plant. International Journal of Current Pharmaceutical Research 2019; 11(5): 1-13.

[85] Kolak, U, Hacıbekiroğlu I, Boğa M, Özgökçe F, Ünal M, Choudhary MI and Ulubelen A. Phytochemical investigation of *Leontice leontopetalum* L. subsp. *ewersmannii* with antioxidantand anticholinesterase activities. Records of Natural Products 2011; 5(4): 309-313.

[86] Al-Snafi AE. Constituents and pharmacological effects of *Leontice leontopetalum*- A review. To Chemistry Journal 2019; 3: 103-108.

[87] Hasimi N, Ertaş A, Oral EV, Alkan H, Boğa M, Yılmaz MA, Yener I, Gazioğlu I, Ozaslan C, Akdeniz M and Kolak U. Chemical profile of *Malva neglecta* and *Malvella sherardiana* by Lc-MS/MS, GC/MS and their anticholinesterase, antimicrobial and antioxidant properties with aflatoxincontents. Marmara Pharmaceutical Journal 2017; 21(3): 471-484.

[88] Al-Snafi AE. Medical benefit of *Malva neglecta*- A review. IOSR Journal of Pharmacy 2019; 9(6): 60-67.

[89] Ionita R, Postu PA, Mihasan M, Gorgan DL, Hancianu M, Cioanca O and Hritcu L. Ameliorative effects of *Matricaria chamomilla* L. hydroalcoholic extract on scopolamine- induced memory impairment in rats: A behavioral and molecular study. Phytomedicine 2018; 47: 113-120.

[90] Marek CB, Itinose AM, Jorge TCM, Parizotto RA, Tebaldi NR and Reichert AM. Influence of leaf extracts from *Melia azedarach* L. on butyrylcholinesterase activity in rat liver. Journal of Medicinal Plants Research 2012; 6(22): 3931-3938.

[91] Ozarowski M, Mikolajczak PL, Piasecka A, *et al*. Influence of the *Melissa officinalis* leaf extract on long-term memory in scopolamine animal model with assessment of mechanism of action. Evid Based Complement Alternat Med 2016; 9729818.

[92] Dastmalchi K, Ollilainen V, Lackman P, *et al*. Acetylcholinesterase inhibitory guided fractionation of *Melissa officinalis* L. Bioorg Med Chem 2009; 17(2): 867-871.

[93] Zouari-Bouassida K, Trigui M, Makni S, Jlaiel L and Tounsi S. Seasonal variation in essential oils composition and the biological and pharmaceutical protective effects of *Mentha longifolia* leaves grown in Tunisia. Biomed Res Int 2018; 7856517.

[94] Ertaş A, Gören AC, Haşimi N, Tolan V and Kolak U. Evaluation of antioxidant, cholinesterase inhibitory and antimicrobial properties of *Mentha longifolia* subsp. *noeana*and its secondary metabolites. Rec Nat Prod 2015; 9(1): 105-115.

[95] Tumen I, Senol FS and Orhan IE. Inhibitory potential of the leaves and berries of *Myrtus communis* L. (myrtle) against enzymes linked to neurodegenerative diseases and their antioxidant actions. Int J Food Sci Nutr 2012; 63(4): 387-392.

[96] Lopez S, Bastida J, Viladomat F and Codina C. Acetylcholinesterase inhibitory activity of some Amaryllidaceae alkaloids and Narcissus extracts. Life Sci 2002; 71(21): 2521-2529.

[97] Karakoyun C and Unver-Somer N. Simultaneous quantitative analysis of biologically important Amaryllidaceae alkaloids in *Narcissus tazetta*L subsp. *tazetta*by HPLC/ PDA. J Res Pharm 2019; 23(3): 498-505.

[98] Orhan I and Şener B. Sustainable use of various Amaryllidaceae plants against Alzheimer's disease. Proc WOCMAP III. Vol. 4: Targeted Screening of MAPs, Economics & Law. Eds. C Franz, Á Máthé, LE Craker and ZE Gardner. ActaHort 2005: 678.

[99] Al-Snafi AE. Constituents and pharmacology of *Narcissus tazetta*. IOSR Journal of Pharmacy 2020; 10(9): 44-53.

[100] Topcagic A, Cavar Zeljkovic S, Karalija E, Galijasevic S and Sofic E. Evaluation of phenolic profile, enzyme inhibitory and antimicrobial activities of *Nigella sativa* L. seed extracts. Bosn J Basic Med Sci 2017; 17(4): 286-294.

[101] Ansari M, Mandegary A, Mosalanejhad N, Asadi A and Sharififar F. *Nigella sativa* L., supplementary plant with anticholinesterase effect for cognition problems: A kinetic study. Curr Aging Sci 2019 doi: 10.2174/1874609812666190808153246.

[102] Ali Sk, Hamed AR, Soltan MM, Hegazy UM, Elgorashi EE, El-Garf IA and Hussein AA. *In vitro* evaluation of selected Egyptian traditional herbal medicines for treatment of Alzheimer disease. BMC Complementary and Alternative Medicine 2013; 13: 121.

[103] Liu W, Zhu Y, Wang Y, Qi S, Wang Y, Ma C, Li S, Jiang B, Cheng X, Wang Z, Xuan Z and Wang C. Anti-amnesic effect of extract and alkaloid fraction from aerial parts of *Peganum harmala* on scopolamine-induced memory deficits in mice. J Ethnopharmacol 2017; 204: 95-106.

[104] Menichini F, Tundis R, Loizzo MR, Bonesi M, Marrelli M, Statti GA, Menichini F and Conforti F. Acetylcholinesterase and butyrylcholinesterase inhibition of ethanolic extract and monoterpenes from Pimpinellaanisoides V Brig. (Apiaceae). Fitoterapia 2009; 80(5): 297-300.

[105] Zhao C, Zhang C, He F, Zhang W, Leng A and Ying X. Two new alkaloids from *Portulaca oleracea* L. and their bioactivities. Fitoterapia 2019; 136: 104166.

[106] Xiu F, Li X, Zhang W, He F, Ying X and Stien D. A new alkaloid from *Portulaca oleracea* L. and its antiacetylcholinesterase activity. Nat Prod Res 2019; 33(18): 2583-2590.

[107] Chen YX, Li GZ, Zhang B, Xia ZY and Zhang M. Molecular evaluation of herbal compounds as potent inhibitors of acetylcholinesterase for the treatment of Alzheimer's disease. Mol Med Rep 2016; 14(1): 446-452.

[108] Ma Y, Li X, Zhang W, Ying X and Stien D. A trace alkaloid, oleraisoindole A from *Portulaca oleracea* L. and its anticholinesterase effect. Nat Prod Res 2021; 35(2): 350-353.

[109] Uysal S, Zengin G, Locatelli M, Bahadori MB, Mocan A, Bellagamba G, De Luca E, Mollica A and Aktumsek A. Cytotoxic and enzyme inhibitory potential of two *Potentilla* species (*P. speciosa*L. and *P. reptans* Willd.) and their chemical composition. Front Pharmacol 2017; 8: 290.

[110] Vahedi-Mazdabadi Y, Karimpour-Razkenari E, Akbarzadeh T, Lotfian H, Toushih M, Roshanravan N, Saeedi M and Ostadrahimi A. Anti-cholinesterase and neuroprotective activities of sweet and bitter apricot kernels (*Prunus armeniaca* L.). Iran J Pharm Res 2020; 19(4): 216-224.

[111] Wojdyło A and Nowicka P. Profile of phenolic compounds of *Prunus armeniaca* L. leaf extract determined by LC-ESI-QTOF-MS/MS and their antioxidant, anti-diabetic, anti-cholinesterase, and anti-Inflammatory potency. Antioxidants (Basel) 2021; 10(12): 1869.

[112] Taghizadeh SF, Asgharzadeh A, Asili J, Sahebkar A and Shakeri A. Evaluation of total phenolic content and antioxidant activity in ten selected mahaleb (*Prunus mahaleb* L.) genotypes. International Journal of Horticultural Science and Technology 2015; 2: 187-197.

[113] Suh SJ, Koo BS, Jin UH, Hwang MJ, Lee IS and Kim CH. Pharmacological characterization of orally active cholinesterase inhibitory activity of *Prunus persica* L. Batsch in rats. J Mol Neurosci 2006; 29(2): 101-107.

[114] Boğa M, Ertaş A, Yeşil Y, Haşimi N, Yılmaz MA and Özaslan C. Phytochemical analysis and antioxidant and anticholinesterase activities of *Pulicaria dysenterica* from Turkey. DUFED 2014; 3(1): 53-60.