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A review study on medicinal plants affecting amnesia through cholinergic system

Azar Baradaran[1], Zahra Rabiei[2], Mortaza Rafieian[3], Hedayatollah Shirzad[2,*]

[1]Department of Clinical Pathology, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3]Isfahan Governer Office, Isfahan, Iran

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ABSTRACT

Neurotransmitter modification is an important method for the treatment of memory loss or amnesia. Cholinomimetic drugs, particularly, acetylcholine esterase inhibitors are the mainstream in pharmacotherapy of amnesia. Donepezil, tacrine, galantamine, and rivastigmine are cholinesterase inhibitors which are widely used in the treatment of amnesia, however, their therapeutic effects are not significant. Therefore, other possibilities including herbal medicine sources have been considered for memory loss therapy. There are some Medicinal plants with cholinomimetic property which mostly possess antioxidant activity, too. These plants may not only ameliorate amnesia but also can be a good source for drug discovery. In this paper other than introducing the medicinal plants and their components affective on cholinergic system and effective on memory loss, their probable advantages over synthetic drugs are discussed.

Review

Implication for health policy/practice/research/medical education:
Getting familiar with medicinal plants effective on amnesia to make it easy choosing a suitable one for prevention or amelioration of amnesia.

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Introduction

The most important neuroanatomical structures in the brain, involved in memory function include Hippocampus, Cerebellum, Amygdala, Basal ganglia and Cortical structures (1). Neurotransmitter modification in these regions is a method for the treatment of memory loss or amnesia. Acetylcholine esterase inhibition in the treatment of amnesia is the mainstream pharmacotherapy. Donepezil, tacrine, galantamine, and rivastigmine are cholinesterase inhibitors which are widely used in the treatment of amnesia, however their therapeutic effects are not significant (2). Therefore, other possibilities including herbal medicine sources have been considered and evaluated for memory loss therapy. In this paper other than introducing the medicinal plants affective on cholinergic system and effective on memory loss, their probable advantages over synthetic drugs are discussed.

Cholinergic transmission in the brain cortical and hippocampal regions plays a fundamental role in memory (3). Improved cholinergic neurotransmission can be achieved by increasing stimulation of cholinergic receptors and increasing the availability of acetylcholine in the neuronal synaptic cleft. Muscarinic M_2 autoreceptor inhibitors increase the release of acetylcholine (4) while cholinesterase inhibitors decrease the breakdown of acetylcholine. Cholinesterase inhibitors are the most common pharmacotherapy for amnesia, dementia and Alzheimer's disease. Several acetylcholine esterase inhibitors have been approved by the FDA for alleviation of symptoms; however, permanent improvement has not yet been achieved. Tacrine should be used with great caution due to its hepatotoxicity (5,6).

Nowadays, much attention has been paid to medicinal plants and they are considered as a reliable source for searching new drugs.

Beneficial effects of medicinal plants acting on cholinergic nervous system

There are some medicinal plants which alleviate memory function by increasing cholinergic activities, the same as

*Corresponding author: Hedayatollah Shirzad, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran. E-mail: shirzadeh@yahoo.com

synthetic drugs. Medicinal plants usually have antioxidant activity, therefore, they should be preferred to synthetic drugs, if they show high efficacy in amnesia.

It has been suggested that antioxidants promote health and ameliorate amnesia. However, clinical trials with a limited number of antioxidants have shown limited efficacy and even sometimes harmful effects have been reported (7). It seems that regimens with high vegetables and fruits due to variety in antioxidant activities are nearly almost beneficial, however, diet supplementations with limited number of antioxidants mostly are not effective. Diets with high plants antioxidants have a mixture of antioxidants and they work as a continuous chain to reduce oxidative stress. However, when one or two substances are used, the antioxidant chain is not completely available to continually combat oxidative stress (2,8). It is known that following scavenging a free radical, if the antioxidant is not restored, it might become a prooxidant. In this situation, the effect of such antioxidant might be no or a damaging effect (7). Therefore, in antioxidant therapy, plants antioxidants are preferred.

In conclusion, plants which usually possess antioxidant property, if increase cholinergic activity might be *per se* or in combination with other cholinergic activators a good choice for the treatment of amnesia. The following are medicinal plants with cholinomimetic activities which other than being used as anti-amnesic drugs; they might be reliable sources for investigating new drugs (Table 1).

Medicinal plants and their derivatives with cholinomimetic activity

***Acorus gramineus*:** It has been shown that memory and learning functions were improved in ibotenic acid-induced decrease of acetylcholine estragenic neurons in the hippocampus of rats by dried rhizome of *Acorus gramineus* in Morris Water maze (9).

Angelica gigas has been able to significantly ameliorate the scopolamine-induced amnesia in passive avoidance and Morris water maze tests. The anti-amnesic activity was inhibited by acetylcholine esterase activity in the hippocampus (10). A coumarin isolated from the *A. gigas* (Nodakenin) was able to antagonize the scopolamine-induced cognitive impairments in passive avoidance and Y-maze tests. The escape latency during training (in the Morris water maze test) was reduced whereas swimming times and distances within the target zone were increased in the nodakenin-treated amnesic group. Nodakenin exhibited an inhibitory effect on acetylcholine esterase activity in both *ex vivo* and *in vitro* studies. It is suggested that nodakenin conferred beneficial effect against cognitive impairment through enhancement of cholinergic signaling (11). In summary, nodakenin is a promising anti-amnesia agent (12).

Chong–Myung–Tang (CMT) is one of the traditional Korean herbal medicines, consisting Acorus gramineus Soland, Poria cocos Wolf and Polygala tenuifolia Willdenow used for the therapy of learning and memory improvement. Administration of CMT significantly restored memory impairments induced by scopolamine in the passive avoidance test and also reduced escape latency during trial sessions in the Morris water maze test. The increased acetyl cholinesterase activity produced by scopolamine was significantly inhibited by CMT (13).

Cnidium officinale and *Angelica sinensis*: *n*-Butylidenephthalide (BDPH) is a lipophilic ingredient of *C. officinale* and *A. sinensis*. BDPH was able to attenuate scopolamine (a peripheral cholinergic muscarinic receptor antagonist) induced acquisition impairment. Scopolamine did not inhibit the counteracting effect of BDPH against scopolamine-induced acquisition impairment. BDPH attenuated a central acetylcholinergic neurotoxin (AF64A) induced cognitive impairment. These findings may suggest that the cognitive enhancing effect of BDPH should act through the activation of the central muscarinic and nicotinic receptors (14).

***Coptis chinensis*:** Berberine isolated from *C. chinensis*, was shown to attenuate scopolamine-induced amnesia significantly. The beneficial effect was suggested to be linked to the increase in peripheral and central cholinergic neuronal system activities (15).

***Corydalis yanhusuo*:** Pseudocoptisine, a quaternary benzylisoquinoline alkaloid isolated from *C. yanhusuo* has been shown to confer anti-amnesic activity of scopolamine-induced memory and learning impairments. This effect was related partially to inhibition of acetylcholine esterase activity in a dose-dependent manner (16). It has been shown that the detected acetylcholine esterase inhibitory activity might be traced back to the presence of a benzylisoquinoline alkaloid.

***Cnidium monnieri*:** Osthole, a compound isolated from *C. monnieri, has been able to* reverse the scopolamine-induced performance deficit in ovariectomized rats by mediating the activation of the central cholinergic neuronal system (17).

***Crocus sativus*:** Intracerebroventricular (ICV) injection of streptozotocin (STZ) causes cognitive impairment in rats. The beneficial effect of *Crocus sativus* L. extract was evaluated on STZ-induced memory, learning and cognitive impairment in male rats. The memory and learning performance was assessed using passive avoidance paradigm, and for spatial cognition evaluation, Y-maze task was used. It was found that CSE-treated STZ-injected rats show higher correct choices and lower errors in Y-maze than vehicle-treated STZ-injected rats. In addition, CSE administration significantly attenuated learning and memory impairment in treated STZ-injected group in passive avoidance test. Reports on antagonizing action of CSE on scopolamine-induced memory deficits support the direct or indirect hypothesis of its cholinergic mimicking action (18).

***Desmodium gangeticum*:** The aqueous extract of *Desmodium gangeticum* has been shown to reverse scopolamine induced amnesia by decreasing whole brain acetylcholine esterase activity (19).

***Foeniculum vulgare*:** The methanolic extract of *F. vulgare* has been shown to ameliorate the amnesic effect of scopolamine by inhibiting acetylcholine esterase and increasing step-down latency activities (20).

***Geissospermum vellosii*:** Pretreatment with the ethanolic extract of *G. vellosi* stem barks has been shown to reduce scopolamine-induced memory loss as evidenced in Morris water maze and passive avoidance tests. *G. vellosii* has shown potent anticholinesterase activity *in vitro* with a mean IC_{50} value of 39.3 µg/mL where geissospermine was identified as the main cholinesterase inhibitor (21).

***Ginkgo biloba*:** Pretreated with *G. biloba* extract has been resulted in significant inhibition of acetylcholine esterase activity in rodent (22). It has been shown that the reduced acetylcholine esterase activity could increase acetylcholine level, hence, increase the learning and memory functions. The most pronounced acetylcholine esterase inhibition was found in the detergent soluble fraction mainly consisting of the G4 form

of the acetylcholine esterase of *G. biloba*, rather than the salt soluble fraction which mainly consisting the G1 isoform of the acetylcholine esterase. This may imply that the G4 isoform of acetylcholine esterase is important in maintaining memory and learning functions.

***Huperzia serrata*:** (−)-Huperzine A is a natural *Lycopodium* alkaloid which is usually extracted from *H. serrata*. It has been reported that (−)-huperzine A has a unique anti-acetylcholine esterase activity. Pretreatment of rats with (−)-huperzine A before scopolamine injection resulted in improvement of reference memory and working memory, as shown in radial maze performance (23).

***Ligusticum wallichii and Angelica sinensis*:** Ferulic acid, isolated from *L. wallichii and A. sinensis is able to* reverse the cycloheximide- and scopolamine- induced cognitive impairment but not the *p*-chloroamphetamine-induced impairment by activation of the cholinergic system and enhancement of brain microcirculation. *p*-Chloroamphetamine destroys the cells, however, cycloheximide and scopolamine inhibit them (24).

***Lonicera japonica*:** Luteolin is usually found in perilla leaf and seed, celery, green pepper, *L. japonica* and chamomile tea. Luteolin has been able to reverse learning acquisition impairment induced by cholinergic inhibitor, scopolamine hydrobromide, or nicotinic receptor antagonists. However, luteolin does not protect the brain from learning acquisition impairment induced by dopaminergic neurotoxin (6-hydroxydopamine, 6-OHDA), *N*-methyl bromide and serotonergic neurotoxin (5,7-dihydrotroptamine, 5,7-DHT). These findings may suggest that luteolin might be able to protect the brain from scopolamine-induced learning acquisition impairment by enhancing the activities of central nicotinic and muscarinic receptors (25). Luteolin has also been shown to confer robust neurovascular protection in Abeta induced amnesia as evidenced by improvement in spatial learning and memory capabilities. This effect has been attributed to increased regional cerebral blood flow, efficient clearance of reactive oxygen species, a modulated microvascular function, restored acetylcholine level and reduced acetylcholine esterase activity, as well as increased brain-derived neurotrophic factor level and its receptor tyrosine kinase B expression in cerebral cortex (26).

***Murraya koenigii*:** The leaves of *M. koenigii* has been able to alleviate scopolamine-induced amnesia in young (3-4 months) and aged (12-15 months) mice. Inhibited brain cholinesterase activity has been attributed to this protection (27).

***Nardostachys jatamansi*:** The ethanolic extract of *Nardostachys jatamansi* was shown to reverse diazepam- or scopolamine-induced amnesia. This improvement has been attributed to facilitated cholinergic transmission and its antioxidant property (28).

***Nelumbo nucifera*:** The aqueous extract of *N. nucifera* semen has been shown to attenuate scopolamine-induced deficit in which the acetylcholine esterase activity of the *N. nucifera* treated group decreased to 7.35 % and CHAT-positive neurons in the *N. nucifera* treated group increased by 51.02 % compared with the control group. By inhibiting acetylcholine esterase activity and inducing CHAT expression, *N. nucifera* conferred anti-amnesic protection (29).

***Origanum vulgare*:** The intra-hippocampal injection of Origanum aqueous extract improves the rat working memory in Morris water maze. *Origanum vulgare L. ssp. Viridis* (ORG) is a rich source of antioxidants and antiacetylcholinesterase. Acid ursolic in this plant has been shown to have antiacetylcholinesterase activity (30).

***Panax ginseng*:** Ginsenosides are the saponins of ginseng which are extracted from the rhizome and root of *P. ginseng*. The neuroprotective effects of ginsenosides have been widely studied in different models of neurological deficits such as parkinson's disease, cerebral ischemia and memory impairments. Ginsenoside Rg1 is able to increase the amplitude of long-term potentiation and improve synaptic transmission (31,32). It has been revealed that ginsenosides Rg1 and Rb1 are able to enhance central nervous system (CNS) cholinergic metabolism. They are also able to potentiate the cholinergic system by (1) enhancing the level of acetylcholine in the CNS (through increasing acetyltransferase activity or inhibiting acetylcholine esterase activity and (2) increasing the density of central M-cholinergic receptors (33,34). Ginsenoside Rg1, panaxatriol with two sugars, is generally more nootropic than Rb1, panaxadiol with four sugars. Increased protein biosynthesis as evidenced in the mouse brain may contribute to the memory consolidative effect conferred by ginsenosides Rb1 and Rg1 (35).

***Polygala tenuifolia*:** *Polygala tenuifolia* is used for the treatment of noctural emission, neurasthenia, palpitation and amnesia. It has been shown to ameliorate the scopolamine-induced decrease of retention in passive avoidance by enhancing the central cholinergic system (36).

***Pueraria lobata*:** Puerarin, isolated from *P. lobata*, has been shown to attenuate *p*-chloroamphetamine, mecamylamine or dizocilpine induced inhibitory avoidance performance deficits but not the scopolamine-induced one. The beneficial effect of puerarin has been attributed to the enhanced cholinergic activity via nicotinic but not muscarinic receptors as well as activated NMDA receptors and decreased serotonergic neuronal activity (37).

***Pueraria thunbergiana*:** Daidzein isolated from *P. thunbergiana* inhibited scopolamine-induced amnesia in the Y-maze test by acting as a choline acetyltransferase activator for acetylcholine biosynthesis (38). The precise mechanisms for daidzein for enhancement remain largely unclear. However, it seems to act as catecholamine transferase activator and one of the active ingredients responsible for memory enhancement. Since only the cholinergic pathway has been studied studied, it remains unknown whether daidzein act through a single direct action at the cholinergic system or act at multiple action sites.

Rhizoma coptidis : Berberine is the major alkaloidal component of *Rhizoma coptidis*, and has multiple pharmacological effects such as inhibiting acetylcholinesterase. The Alzheimer model was established by injecting Abeta (5 microgram) into the rats hippocampuses bilaterally and the spatial memory was assayed by Morris water maze test. Intragastric administration of berberine significantly ameliorated the spatial memory impairment and increased the expression of IL-1beta, iNOS in the rat model of Alzheimer disease (39).

***Salvia miltiorrhiza*:** Tanshinones, isolated from the roots of *S. miltiorrhiza,* are a group of diterpenoids. 15, 16-dihydrotanshinone, tanshinone I, tanshinone IIA and cryptotanshinone are collectively called tanshinone congeners. All these diterpenoids reversed the cognitive impairment induced by scopolamine. Cryptotanshinone and 15,16-dihydrotanshinone I were proven to induce an inhibitory effect on acetylcholine esterase in *ex vivo* and *in vitro* studies. Tanshinone congeners may exert a beneficial effect on cognitive

Table 1. Medical plants and their derivatives acting through cholinergic system

Scientific name	Active ingredient involved	Mechanism	The models used	Reference
Acorus gramineus, Polygala tenuifolia, and Poria cocos	CMT	Antiacethylcholine esterase activity	Scopolamine (2 mg/kg), in mouse)	(9,21)
Angelica gigas	Decursin, Nodakenin	AChE Inhibition	Scopolamine (1 mg/kg, ip), in mice	(22,23)
Coptis chinensis	Berberine	Cholinergic activity	Scopolamine (1.0 mg/kg, ip), in rats	(15)
Crocus sativus	Aqueous extract	Cholinergic mimicking action	ICV injection of streptozotocin (STZ)	(17)
Corydalis yanhusuo	Pseudocoptisine	AChE inhibition	Scopolamine (1.0 mg/kg, ip), in mice	(16)
Desmodium gangeticum	Extract	Inhibition of AChE activity	Scopolamine (0.4 mg/kg, ip), in mice	(19)
Geissospermum vellosii	Extract	Anticholinesterase activity	Scopolamine (1.0 mg/kg, ip), in mice	(21)
Ginkgo biloba	Extract	AChE inhibition, in vitro	Scopolamine (3.0 mg/kg, ip), in mice	(22)
Ginkgo biloba	Extract	Cholinergic and histaminergic enhancement	Scopolamine (0.5 mg/kg, ip), in rats	(36)
Liuwei dihuang	Extract	Activation of cholinergic system	Cycloheximide (1.5 mg/kg, sc), in rats	(38)
Lonicera japonica	Luteolin	Enhanced muscarinic and nicotinic receptors activity	Scopolamine (0.5 mg/kg, ip), in rats	(40)
Melissa officinalis	Extract	Antiacethylcholine esterase and antioxidant effects	Scopolamine (1 mg/kg, ip)	(41)
Murraya koenigii	Extract	Cholinesterase inhibition	Scopolamine (0.4 mg/kg, ip), in mice	(27)
Nardostachys jatamansi	Ethanolic extract	Cholinergic transmission	Scopolamine (0.4 mg/kg, i. p.) or diazepam (1.0 mg/kg, i. p.)	(28)
Nelumbo nucifera	Extract	ACHE inhibited and increased CHAT expression	Scopolamine (1 mg/kg, ip), in rats	(29)
Paeonia lactiflora	Extract	Reversed scopolamine-induced decrease in ACh content	Scopolamine (0.3 mg/kg, ip), in rats	(48)
Polygala tenuifolia	Extract	Enhanced central cholinergic system	Scopolamine (0.2 mg/kg), in mice	(37)
Polygala tenuifolia	Tenuifoliside B	Central cholinergic system	Scopolamine (1.0 mg/kg), in rats	
Pueraria lobata	Puerarin	Cholinergic activity via nicotinic receptors	Mecamylamine (10 mg/kg, ip); p-chloroamphetamine (5 mg/kg, ip) or dizocilpine (0.1 mg/kg, ip), in rats	(37)
Pueraria thunbergiana	Extract	Activation of acetyltransferase, in vitro	Scopolamine (1.0 mg/kg, sc), in mice	(38)
Salvia triloba	Extract	Antiacethylcholine esterase and antioxidant effects	Scopolamine (1 mg/kg, ip)	(51)
Rhizoma coptidis	Alkaloid fraction	Inhibiting acetylcholinesterase, anti-inflammation	Injecting Abeta (5 mcg) into the rats hippocampuses bilaterally	(52)
Rosmarinus officinalis	Rosmarinic acid	antioxidant activity	ICV injection of Aβ 25–35 in mouse	(53)
Salvia triloba	Extract	AChE inhibited	Scopolamine (1.0 mg/kg, ip), in mice	(41)
Schisandra chinensis	Gomisin A	AChE inhibition	Scopolamine (1 mg/kg, ip), in mice	(44)
Scrophularia buergeriana	(2)8-O-E-p-methoxycinna moylharpagide (MCA-Hg)	Inhibited activity of AChE within the cortex and hippocampus	(Scopolamine (1 mg/kg, ip	(42)
Silybum marianum	Etract	Antiacethylcholine esterase, antioxidant effects	ibotenic injection in NBM	(44)
Teucrium polium	Extract	Antiacethylcholine esterase and antioxidant effects	Scopolamine (1 mg/kg, ip)	(42)
Teucrium polium	Extract	Inhibited AChE activity	Scopolamine (1.0 mg/kg, ip), in mice	(47)
Thespesia populnea	Extract	Anticholinesterase activity	Scopolamine (0.4 mg/kg, ip), in mice	(48)
Tremella fuciformis	Extract	Cholinergic system	Scopolamine (2 mg/kg, sc), in rats	(49)
Uncariae ramulus	Extract	Reduced the loss of cholinergic immunoreactivity in the hippocampus	Ibotenic acid (0.1 µL at 4 µg/µL, icv), in rat	(54)
Ziziphus mauritiania	extracts	Inhibition of AChE activity	Scopolamine in rats	(50)

impairment by cholinergic signaling enhancement (40).

***Salvia triloba*:** The hydroalcoholic extract of *Salvia triloba* enhances memory effect function partially through acetylcholine esterase inhibition and partially through radical scavenging activity (41).

Salvia lavandulaefolia* and *Salvia officinalis: There are some reports on anticholinesterase activities of some *Salvia* species such as *Salvia lavandulaefolia* and *Salvia officinalis*. Furthermore, alpha-pinene and 1,8-cineole, the monoterpene type of components, were found to inhibit acetyl cholinesterase in uncompetitive and reversible manner acting synergistically and, therefore, responsible for inhibitory effect of the essential oil of *Salvia* species (42).

***Scrophularia buergeriana*:** *Scrophularia buergeriana* enhances cognition by inhibiting the activity of acetylcholine esterase within the cortex and hippocampus to a level similar to that observed in donepezil-treated rats/mice (42). *E-p*-methoxycinnamic acid (*E-p*-MCA), a phenylpropanoid isolated from roots of *S. buergeriana*, improved impairments of spatial learning and memory induced by scopolamine (43). Although the underlying mechanism is not yet fully elucidated, the α,β-unsaturated carboxyl moiety and the *para*-methoxy group in *E-p*-MCA are postulated to be crucial components in cognition-enhancing activity.

***Schizandra chinesis*:** Gomisin A, an ingredient of *S. chinesis*, improved the cognitive impairment induced by scopolamine in Morris water maze, passive avoidance test and Y-maze test. The cognition-enhancing effect of gomisin A is dose-dependently through inhibition of acetylcholine esterase activity (44).

***Silybum marianum*:** S. marianum has a protective effect on the nerve tissue in a mouse model of Alzheimer's disease by decreasing of the GFAP protein synthesis in hypocampus and lead to the improvement of behavioral performance. The ELISA method showed that the level of the GFAP synthesis decreased in the experimental group compared to the NBM-lesioned group (45).

Soybean, *Glycine max* (L.), known as golden bean, contains vegetable protein, oligosaccharide, dietary fiber, vitamins, isoflavones and minerals. Consumption of soybean in diet may not only improve memory but also reverse the memory deficits, owing to its multifarious activities. Passive avoidance paradigm and elevated plus maze served as exteroceptive behavioral models for testing memory. Alprazolam (0.5 mg/kg; *i.p.*) induced amnesia served as interoceptive behavioral model. The administration of soybean significantly reversed alprazolam-induced amnesia in a dose-dependent manner as indicated by the increased step down latency of mice using passive avoidance paradigm and increased transfer latency using elevated plus maze. Soy isoflavones are reported to increase cholinergic transmission due to indirect facilitation of acetylcholine in the brain. This increased cholinergic transmission may be exerted through inhibition of acetylcholinesterase activity or activation of choline acetyltransferase (46).

Teucrium polium: In the anticholinesterase assay, the extracts showed similar inhibitions against acetylcholinesterase and *Teucrium polium* had the highest inhibition (65.8% at 1.0 mgml−1). This plants to appraise their effectiveness in learning and memory, which used antiamnesic activity assay in mice induced by scopolamine, a non-selective muscarinic cholinergic receptor antagonist (42). An ethanolic extract of *T. populnea* reversed the scopolamine-induced amnesia through reduced brain cholinesterase activity. *Thespesia populnea* has antifertility, antibacterial, anti-inflammatory, hepatoprotective and antioxidant activities, too (47).

***Tremella fuciformis*:** *T. fuciformis* reduces scopolamine-induced learning and memory deficits by increasing the central cholinergic activity in the medial septum and hippocampus. The water extract of *T. fuciformis* also promotes neurite outgrowth of PC12h cells. The anti-amnesic effect of *T. fuciformis* has been conferred partly through the cholinergic system and promotion of neuritogenesis. Neurogenesis has been demonstrated to play a crucial role in regulating memory and learning (48).

***Uncariae ramulus*:** The methanolic extract of *Uncariae ramulus* induces significant reversals of ibotenic acid-induced deficit in learning and memory by reducing the loss of cholinergic immunoreactivity in the hippocampus (49).

***Ziziphus mauritiana**: The* extracts of *Z. mauritiana* seeds impaired spatial recognition of rodents, the activity of which was greatly produced by the portion extracted by ethyl acetate. Spatial memory as measured by the Y-maze tests is dependent on hippocampal learning and memory function and is related to the NMDA receptor/Ca2+ influx signaling pathway. It is possible that, compounds contained in the ethyl acetate portion of the extract may inhibit this hippocampal NMDA receptor/Ca2+ signaling pathway. Seeds of *Z. mauritiania* extracted with ethyl acetate not only impair the acquisition but also consolidation and retrieval of spatial recognition memory in animals in the Y- maze (50).

Authors' contributions

MR and ZR prepared the main draft, AB and HSh edited the paper.

Conflict of interests

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Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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