Neuroprotective Effects of Medicinal Plants and Their Constituents on Different Induced Neurotoxicity Methods: A Review

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A B S T R A C T

In the traditional medicine, numerous plants have been used to treat cognitive disorders. Natural products play an essential role in prevention and therapy of various neurodegenerative diseases, and neuronal dysfunctions. Different studies suggest that natural products, such as polyphenolic and alkaloids compounds that isolated from plants potentially delayed the neurodegeneration and also improve memory and cognitive function. Ethno pharmacological studies have provided information to identify potential new drugs from plant sources. Recently many drugs which available in medicine were originally isolated from plants or their constituents including, anticholinesterase (Anti-ChE) alkaloids isolated from plants have been investigated for their potential in the treatment of Alzheimer's disease (AD). Anti-inflammatory and antioxidant activities of plants and isolated components form plants were used in improvement neuro-inflammation, anxiety, convulsion and etc. Medicinal plants have beneficial properties due to presence of various complex chemical substances for treatment of toxicity in the nervous system. This review article evaluated the some of the medicinal plants and their active constituents that have been used in different methods induced neurotoxicity.

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Introduction

In the neurodegenerative diseases, central nervous system (CNS) are lost leading to either functional loss or sensory dysfunction [1]. Nowadays, these diseases, which are associated with different multifactorial etiologies, have created massive medical, social, and financial problems [2]. The pathological signs of neurodegenerative disorders are aging, disability and mortality. The neurodegenerative diseases are including Alzheimer's Disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS) and *etc.* [1, 2]. Irreversible memory impairment, cognitive and behavioral disturbances are prevalent AD symptoms [3].

Pathologic processes including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, and genetic factors lead to neuronal degeneration in PD [4]. Laboratory analysis of patients brain have shown that elevated lipid peroxidation may destroy cholinergic neurons in AD [5] and dopaminergic neurons in PD [6]. There are different antioxidants in the brain, like superoxide dismutase (SOD) as enzymatic antioxidant [7] and thiol containing molecules such as glutathione (GSH) as non-enzymatic antioxidant [8]. CNS which contains high level of polyunsaturated fatty acids is more sensitive to peroxidation reactions (9). But, CNS is not particularly enriched in antioxidant defenses. Human brain has high levels of ascorbate in general and iron in certain regions. Actually, antioxidant activity of the brain is lower than other tissues. So, neural cells are more susceptible than other tissues to oxidative damage [9].

In herbal medicine, plant organs including: leaves, stems, roots, flowers, fruits and seeds were used as alternative and complementary therapy. Some herbs which are include resveratrol, curcumin, ginsenoside, polyphenols, triptolide, *etc.* which have neuroprotective characteristic [10]. Herbal products contain of complex active components or phytochemicals like flavonoids, alkaloids and isoprenoids. Therefore, it is frequently difficult to determine which component(s) of the herb(s) has more biological activity [11, 12]. In the present review study, it was aimed to highlight the useful effects of different plants and their constituents on different induced methods for neurotoxicity.

Materials and Methods

The data of this review article was collected by searching only in English language for the keywords " Medicinal plants", " extract", " neurotoxicity ", " plants constituent " and " neuroprotective effect " in databases namely ISI Web of Knowledge, Medline/ Pubmed, Science direct, Scopus and Google Scholar. The published papers until Jan 2016 were considered.

Results

Salvia officinalis L. one of the members of the family Lamiaceae is used against degenerative diseases such as brain dysfunction and declining mental functions [13]. The pharmacological leaves of this plant due to the presence of flavonoids, phenolic compounds [14] have anti oxidative properties [15]. The leaves of *Salvia officinalis* ethanolic extract decreased malondialdehyde (MDA) levels, Also this extract increased activity of brain acetylcholinesterase and glutathione (GSH) levels in STZ injected rats [16]. Treatment of male rats with *Salvia officinalis* nanoparticles decreased reactive oxygen species (ROS) production and increased glutathione peroxidase (GPx) activity in the cerebral cortex injected MeHg rats [17]. Flavonoids, as natural neuroprotective polyphenol compounds, are attributed to a variety of biological activities due to their anti-inflammatory and anti-apoptotic activities [18].

Hypericum perforatum

Phenolic content*s of Hypericum perforatum* alcoholic extract have significant neuroprotective effect [19]. Alcoholic extract of *Hypericum perforatum* is very effective in treatment of depression [20], lipid peroxidation decreasing and cell protecting against Amyloid- β induced toxicity [21]. The ethanolic extract of aerial parts of *Hypericum perforatum* can regulate neurotransmitters receptors like D_2 and $5-HT_{2A}$ [22]

Lavandula angustifolia

Researches indicate that *Lavandula angustifolia* can put down and glutamate-induced neurotoxicity via inhibition cholinesterase [23]. It has been reported that *Lavandula angustifolia* extract is benefit for cognitive dysfunction [24].

Opuntia ficus-indica

The fruits and stems of *Opuntia ficus-indica* have been reported that to exhibit antioxidant actions [25]. The methanol extract of this fruits reduced neuronal damage induced by radicals in hippocampal CA1 region of the gerbils and mouse cortical cultures [26]. It was found butanol fraction prepared from *Opuntia ficus-indica* was able to inhibit lipid peroxidation initiated by Fe2+ and L-ascorbic acid in rat brain homogenates [27].

Curculigo orchioides

Curculigo orchioides Gaertn. (Amaryllidaceae family), contains of plentiful cell protective flavonoids and polyphenols [28]. The results of study showed that this plant has cell protective effects in cisplatin-induced cell damage [29]. Similarly *C. orchioides* methanol extract promoted restoration of catalase (CAT), SOD, and GSH levels and decreased MDA levels in cyclophosphamide-induced neurotoxicity [28].

Ficus sycomorus

Different studies reported that some Ficus species have been used for treatment of epilepsy [30]. Anticonvulsant and sedative activity of *Ficus sycomorus* in animal models were also reported [31]. According to the previous studies *Ficus religiosa* has acetylcholinesterase inhibitory [32] and antianxiety [33] activity. Methanolic extract of figs or fruits of this plant showed inhibitory effect in seizures induced by maximum electroshock (MES) and picrotoxin in a dose dependent manner [34]. The Figs contain high amount amino acids [35] and serotonin (5-HT) [34]. Serotonin is useful in protection neurons of induced seizures animals

via modulating GABAergic and glutamatergic neurons [36].

Angelica sinensis

Angelica sinensis is used as sedative pharmacological plant [37]. *Angelica sinensis* extract modulated ROS, MDA and GSH contents in Amyloid β - induced damaged cells. Furthermore, this extract was able to protect cell viability against oxidative stress [38]. Main compounds of *Angelica sinensis* are liguistilide, phthalides, ferulic acid (4-hydroxy-3-methoxycinnamic acid) and polysaccharides [38]. Administration ferulic acid improved Amyloid β- induced memory impairment in mice [39]. Ferulic acid is an antioxidant phenolic compound that protects cells against oxidative stress via conformation changing of synaptosomal membrane proteins [40]. Ferulic acid can scavenge intracellular ROS. It also can increase expression protective genes like heme oxygenase-1 and heat shock protein 72. Therefore, this compound has neuroprotective effect in primary hippocampal cultures against $A\beta_{1-142}$ induced cytotoxicity [41].

Cassia fistula

Hydroalcholic extract of *Cassia fistula* leaf was able to improve injuries in alcohol induced peripheral neuropathy rats [42].

Dichrostachys cinerea

Tribes of Chittoor used *Dichrostachys cinerea* root juice against paralysis [43]. *Dichrostachys cinerea* fruit contains high amounts of phenols, triterpenoids and tannins [44]. Alcoholic extract *Dichrostachys cinerea* has a CNS depressant activity [43]. Saponins, carbohydrates and tannins of *Dichrostachys cinerea* may are responsible of CNS depressant activity [43].

Panax ginseng

Active constituents in most ginseng species, are including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols and fatty acids [45]. *Panax ginseng* (Ginseng) berry ethyl acetate fraction

effectively inhibited the acetylcholinesterase (AChE) activity and decreased MDA levels in mice brain tissues [46]. It has been reported that ginsenoid of *panax ginseng* is responsible of protection of dopaminergic neurons against the neurotoxins MPTP- or 6-OHDA- induced cell degeneration [4]. Ginseng via suppression of neuro-inflammatory processes, releaseing of some neuro-transmitteres and synaptic plasticity regulation has many protective effects on CNS [47]. Ginsenosides have anti-inflammatory [48] and anti-oxidation effects [49] due to ROS, nitric oxide (NO) and tumor necrosis factor-α (TNF-α) suppression.

Aerva lanata

High levels of flavonoids and phenolic compounds maybe are responsible of *Aerva lanata* antioxidant activity [50]. It has been reported that *Aerva lanata* improved behavioral functions [51]. Histological studies on brain showed that administration of *A. lanata* might have a protective effect against cisplatin-induced animals [50].

Juglans regai

Different studies have shown that Walnut species such as *Juglans regai* are containing plentiful of polyunsaturated fatty acids and tocopherols [52]. Fatty acids and vitamin E can improve learning and memory processes [53].

Nigella sativa

Nigella sativa as a medicinal plant is well- known for its potent anti-oxidative effects [54] and also demonstrated that *N. sativa* seeds could preserve significantly the spatial cognitive ability in rats that challenged with chronic cerebral hypo perfusion [55]. Furthermore, *N. sativa* can prevent the damage of spatial memory after scopolamine administration and reduced the AChE activity and oxidative stress of the rats brain [56]. The neuroprotective effects of *N. sativa* and its constituents were reviewed previously [57].

Crocus sativus

In Iranian traditional medicine, *Crocus sativus* had been used to treat cognitive disorders and recently *C. sativus* constituents used for treatment of some neural disorders such as depressant [58, 59]. The effects of *C. sativus* and its constituents on nervous system was also reviewed [58]previously. Crocin, a carotenoid pigment from *C. sativus*, possess potent antioxidant effects by reducing of MDA level [60, 61].

Punica granatum

Potent antioxidants such as polyphenols and tannins which are concentrated in *Punica granatum* L. (pomegranates) can improve degenerative diseases [62]. It was reported that variety of Pomegranate juice can change redox function and ameliorate MPTP-induced neurotoxicity [63]. Administration ethanolic extract of *Pongamia pinnata* decreased lipid peroxidation and increased GSH, SOD, CAT, serum gamma aminobutyric acid levels in stem bark monosodium glutamate-induced neurotoxicity rats [64].

Polygala paniculata

Most species of Polygala genus possesses significant protective effects against neuronal death and cognitive impairments by reduction of Ca^{2+}, Na+ and enhancement of K+ level or 'anti-glutamatergic' effect in neurodegenerative disorders related to excitotoxicity [64]. Bettio reported that some hydroethanolic extract constitutes of *Polygala paniculata* may have considered as ligand for some receptors like 5-HT_{2A}, $α_2$, β and D_2 [65].

Curcuma longa

Some plants such as *Curcuma longa* contain a natural polyphenol and non-flavonoid compound called curcumin. Curcumin is known for its several biological and medicinal effects, such as anti-inflammatory, antioxidant. Curcumin therapeutic potential for neurodegenerative diseases has garnered great interest in recent years [4]. Kulkarni reported that curcumin water soluble extract is able to raise dopamine, norepinephrine and 5-HT levels in CNS [66]. The neuroprotective effects of

curcumin in PD also are related to its antioxidant properties. Wang reported that curcumin repress ROS intracellular accumulation [67] in human cell line SH-SY5Y exposed to 6-OHDA [68]. Administration of curcumin (60 mg/kg, body weight, per oral) for three weeks has amended striatum neuronal degeneration in 6-OHDA lesioned rats [69]. Curcumin via restoration of GSH decreased levels protects of neurons against ROS [70]. Curcumin increased SOD levels in the lesioned striatum of 6-OHDA mice [71] and MES23.5 cells induced the neurotoxin 6-OHDA [67]. Curcumin ,which is able to do Jun N-terminal kinases (JNK) phosphorylation, protects of axons against LPS degeneration [72]. Curcumin neuroprotective effects might be mediated by overexpression of BCl-2 which is inducible nitric oxide synthase (iNOS) antagonist. Therefore, curcumin is effective in improvement of NO-mediated degeneration [73]. Oral administration of 150 mg/kg/day curcumin for 1 week reduced pro-inflammatory cytokines such as interleukin- 6 (IL-6), interleukin-1β (IL-1β), TNF-α and total nitrite generation in the striatum of MPTP-induced mice [74]. Furthermore, curcumin decreased activation of NF-κB in LPS [75] and 6-OHDA-induced inflammatory [67].

The protective effects of some traditional medicinal plants (table 1) and their constituents (table 2) on induced neurotoxicity were summarized.

Table 1. Protective effects of plants extracts on induced neurotoxicity

Plant name	Animal model	Part of plant	Herbal dose	Drug	Dose of drug	Time protocol	Reference
Salvia Officinalis (alcoholic extract)	Rat	leaves	25, 50 and 125 mg/kg, i.p.	Methylmercury	10 mg/kg, i.p.	Administration of extracts for 8 week and drug in first day	[17]
			50, 100 and 125 mg/kg, i.p.	Streptozotocin (STZ)	3mg/kg, ICV, on day 1 and 3	The extract was administered from day 4 to day 21 following first STZ injection	[16]
Hypericum perforatum (hydroalcoholic extract)	Mice	whole plant	300 mg/kg, p.o.	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine	20 mg/kg, i.p.	Drug administrated with an interval of 2 h in the first day and extract for 7 days	[76]
Hypericum perforatum (ethanolic extract)	Hippocampal neurons of rat	top parts	0.606 55.92 6.650 5.846 6.456 8.114 2.947 12.52 μg compound.ml-1)	Amyloid-β peptide (Aβ 25-35)	25 μM	The neurons were exposed to extracts and Aβ for 48 h.	[21]
Lavandula angustifolia (aqueous extract)	Cerebellar granular cell culture of rat	Flower	100 and 1000 μg/ml	Glutamate	10^7 M	Extract administrated 32 min before glutamate, then glutamate added to cell culture	[77]
Opuntia ficus-indica (methanol extract)	Mongolian gerbils	Fruit	0.1, 1 and 4 g/kg, p.o.	Ischemia	5 min	Extract administrated every 24 h for 3 day and Ischemia was induced 2.5 h after the final dose of extract, after reperfusion for 3 h before	[26]
Opuntia ficus-indica (butanol fraction)	Rat cortical cells	stem	1, 3, 10, 100, 300 μg/ml	Oxidative stress, excitotoxins, and Amyloid β (Aβ)	50 μg	First the cultures were exposed to the highest concentration and then serially diluted to the	[27]

						desired concentrations.	
Curculigo orchioides (methanol extract)	Murine model	whole plant	200 and 400 mg/kg,p.o.	Cyclophosphamide	50 mg/kg, i.p.	Administration of extracts for 5 consecutive days and drug in first day	[28]
Ficus religiosa	Mice	Fig	25, 50 and 100 mg/kg, i.p.	Picrotoxin	5 mg/kg, i.p.	Administration of extracts for 30 min before drug injection	[34]
Angelica sinensis (ethanol extract)	Neuroblastoma cells	whole plant	50 and 500 µg/ml	Amyloid β (Aβ)	15 µM	cell were treated with AB in presence of extracts for 48 h	[38]
Cassia fistula (hydroalcoholic extract)	Rat	Leaves	50, 100 and 200 mg/kg, p.o.	Axotomy	-	After axotomy the extracts for 28 consecutive days administrated	[42]
Dichrostachys cinerea (ethanolic extract)	Mice	Root	100, 200 and 400 mg/kg, p.o.	Hot plate	55°C	Jumping time of rats measured on the hot plate before and after the extracts administration	[43]
Panax ginseng (ethanolic extract)	Rat	whole plant	20 mg/kg, p.o.	Acrylamide	50 mg/kg, p.o.	Administration of extract for 11 days and then drug for another 11 days and Vice versa	[78]
Panax ginseng (ethyl acetate fraction)	C57BL/6 Mice	Berry	20 and 50 mg/kg, orally, mixed in drinking water	High-Fat Diet	-	Mice were fed with high-fat diet for 5weeks and then high-fat diet with ginseng berry fraction for 4 weeks	[46]
Aerva lanata (ethanolic extract)	Rat	Aerial parts	250 and 500 mg/kg, p.o.	Cisplatin	5 mg/kg, i.p.	Cisplatin injected in the first day and treatment is continued up to 5 weeks	[50]
Juglans regai (-)	Rat	Fruit	%6	Cisplatin	5 mg/kg, i.p.	Co-administration of walnut and cisplatin for 5 weeks	[79]
Nigella sativa (hydroalcoholic extract)	Rat	Seed	200 and 400 mg/kg ,gavag	Streptozotocin (STZ)	60 mg/kg, i.p.	STZ injected in the first day and treatment is continued up to 6 weeks	[80]

	Rat	Seed	350 mg/kg, p.o.	Ciprofloxacin (CFX)	500 mg/kg, p.o.	Co-administration of CFX and Nigella sativa for 7and 14 days	[81]
	Rat	Seed	350 mg/kg, p.o.	Pentylenetetrazole (PTZ)	60 mg/kg, i.p.	PTZ injected in the first day and treatment with Nigella sativa for 7and 14 days	[81]
Crocus sativus (-)	Mice	pure red styles	60 mg/kg, i.p.	Aluminum	50 mg/kg, orally	aluminum administrated for 5 week and treatment with crocus sativus for the last 6 days of the 5-week Al treatment	[82]
Pomegranate (-)	Rat	Fruit	225 mg/kg,gavag	Methotrexate	20 mg/kg, i.p.	Methotrexate injected in the second day and treatment is continued up to 8 days	[83]
Pomegranate (Juice Extract)	Human Primary Neuronal Cell Cultures	Seeds	1, 10, 50, and 100 μM	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	0.05mM	Cultured neurons were pretreated with each concentrate of extract for 1 hour and then MPTP for 24 hours.	[63]
Pongamia pinnata (ethanolic extract)	Rat	Stem	200 and 400 mg/kg, p.o.	Monosodium glutamate (MSG)	2 g/kg, i.p.	MSG injected for 7 days and extract administrated 1 h after injection of MSG	[64]
Polygala paniculata (hydroalcoholic extract)	Mice	Whole plant	100 mg/kg,gavag	Methylmercury (MeHg)	40 mg/l, freely available	Exposure of MeHg for 2 week and extract administrated twice a day daily.	[84]
Cipura paludosa (ethanolic extract)	Mice	Bulbs	10 and 100 mg/kg,gavag	Methylmercury (MeHg)	40 mg/l, freely available	Exposure of MeHg for 2 week and extract administrated twice a day daily.	[85]

IP: intraperitoneal
ICV: intracerebroventicular
PO: Oral administration (per os)

Table 2. Protective effects of plants constituents on induced neurotoxicity

Plant name	Effective substance	Model of study	Dose of effective substance	Drug and Dose	Time protocol	Reference
Cymbopogon winteri-anus	Citronellol	Albino Swiss mice	(100, 200 and 400 mg/kg, i.p.	Picrotoxin 8 mg/kg (i.p.)	After 60 min of citronellol Administration	[86]
Carum carvi	A,β-epoxy-carvone (EC),	Male mice of Swiss strain	200, 300 or 400 mg/kg	PTZ (60 mg/kg, i.p.)	After 30 min of drug administration	[87]
Mentha spicata L. and *Carum carvi* L.,	Carvone (p-mentha-6,8-dien-2-one)	Rat Cell line	5–20 mm	10 V/0.05–0.1 ms isolated rectangular voltage pulses	After 30 min of drug perfusion	[88]
Crocus sativus	Kaempferol	Mice	100 and 200 mg/kg	Placed In Pyrex cylinders Which were filled with water	24 hours after their first exposure	[59]
	Kaempferol	Rat	50 mg/kg	Placed In Pyrex cylinders Which were filled with water	24 hours after their first exposure	[59]
	Safranal	Mice	0.15 and 0.35 ml/kg,	Sodium pentobarbital, 30 mg/kg, i.p.	Safranal were Administered intraperitoneally, and 30 min afterward, The animals were individually placed at the center of the Plus maze and observed for 5 min	[89]
	Crocin	Rat	15 and 30 mg/kg	STZ-ICV (3 mg/kg)	Three weeks	[90]
	Crocetin	Rat	(25, 50, and 75 , BW, i.p.)	6-Hydroxydopamine (6-OHDA) 10 μg unilateral intrastriatal injection	Locomotion and rotation were observed on day 23 post-injection and after 4 weeks, striatum and substantia nigra were dissected	[91]
Cassia siamea	Barakol	Rat	10, 25, 50, and 75 mg/kg, i.p.	-	Plus-maze 30 min after Barakol injection.	[92]

	Barakol	Rat	25–100 mg/kg, i.p	PTZ (85 mg/kg, s.c.)	30 min before the administration of PTZ	[93]
Galanthus nivalis L.	Galantamine	Cultures of hippocampal and <u>glial cells</u>	1–15 μm	<u>Sodium pentobarbital</u>, 60 mg/kg, i.p.	After an initial stabilization period of 30 min	[94]
	Galantamine	Neuron cell cultures	1 μmol/L	100 μmol/L of NMDA	3-h exposure	[95]
Thymus vulgaris L.	Carvacrol	Rat	73 mg/kg, i.p.	Methotrexate20 mg/kg, i.p.	24 after used of carvacrol, methotrexate was administered	[83]
	Carvacrol	Rat	15 and 20 mg/kg (p.o.)	Cisplatin (CP) 6 mg/kg, i.p.	14 days be- Fore CP injection and for 7 days after CP administration	[96]
	Thymol	Rat	20 mg/kg, (p.o.)	Cisplatin 6 mg/kg, i.p.	14 days be- Fore CP injection and for 7 days after CP administration	[96]
Curcuma longa	Curcumin	Rat	80 mg/kg, (p.o.)	Pilocarpine (380 mg/kg, i.p.)	After 21 days of daily administration	[97]
Nigella sativa	Thymoquinone (TQ)	In vitro (i.v.)	(0.01, 0.1, 1 and 10 μM)	MPP 10 μm on day 10 in vitro (i.v.) For 48 h	On day 8 for 4 days	[98]
	TQ	In vitro	(0.1, 1, 10, 100 nm)	Amyloid b-protein 1–42 (2, 5, 10 lm)	Ab1–42 was Administrat ed to cell cultures with or without TQ on day 13 for 72 h.	[99]
	TQ	Rat	5 mg/kg/day p.o.	Sodium pentobarbital 30 mg/kg, i.p.	TQ was administered 5 days before ischemia and continued during the reperfusion time (7 days).	[100]
	TQ	Rat	2.5, 5 and 10 mg/kg, i.p.	Acrylamide 50 mg/kg/day, i.p.	Administration of TQ 1 week before administration of ACR and Continued during treatment with ACR	[101]
Hipericum perforatum	Quercetin	Rat	25 and 100 mg/kg, ip	Rotenone 2.5 mg/kg, i.p.	60 min before of rotenone injection	[102]

	Quercetin	Rat	50 mg/kg	Sodium Pentobarbital (50 mg/kg, i.p.)	Quercetin Administered (i.p.) Twice,30 min before the first and the second occlusions.	[103]
	Quercetin	Cell line (PC12)	12- 200 µm	6- hydroxydopamine (6-OHDA)	Cells were treated for 6 h with or without different concentrations of quercetin	[104]
	Hypericin	Hacat keratinocytes	2, 5, 10, 15, and 20 µm	Excitation wave- Length of 410 nm.	Exposure to 30 min of ambient light and 24-h incubation	[105]

Conclusion

In this review we intend to concentrate on different induced neurotoxicity in various studies (*in vitro* and *in vivo*) and investigated effects of plants and their constituents on induced toxicity in neural cells. Plants and their constituents play their protective roles via increased SOD and catalase levels, restoration of GSH, decreased MDA levels and also protects of neurons against ROS as antioxidant activities. Anti-inflammatory properties of plants and their constituents as well as due to their interactions with pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α and mediated by overexpression of BCl-2 which is inducible nitric oxide synthase (iNOS). Some protective effects of these natural compounds may be due to reduction of Ca^{2+}, Na+ and enhancement of K+ level or 'anti-glutamatergic' effect. Furthermore, neuroprotective of plants and their components occur via inhibition of the acetylcholinesterase (AChE) activity and decreased MDA levels in the neural system via modulating GABAergic and glutamatergic neurons, and also increasing amount of amino acids and serotonin (5-HT) in the neurotransmitters systems or as ligand for some receptors like 5-HT_{2A}, α_2, β and D_2.

Acknowledgment

Conflict of interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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