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Medicinal Plants with neuroprotective effects

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Abstract

Neuroprotection is the preservation of the structure and function of neurons from insults from cellular injuries caused by a variety of agents or neurodegenerative diseases. Medicinal plants possess neuroprotective effects via mechanisms that include inhibiting protein-based deposit accumulation, oxidative stress, and neuroinflammation, and correcting defects of neurotransmitters such as acetylcholine and dopamine [1-3]. The current review will highlight the neuroprotective effects of medicinal plants.

Keywords: Neuroprotective; Medicinal plants; CNS; Neurons

1. Introduction

Neuroprotection is the preservation of the structure and function of neurons from insults from cellular injuries caused by a variety of agents or neurodegenerative diseases. In recent years, more attention has been paid to traditional medicine. Medicinal plants possess neuroprotective effects via mechanisms that include inhibiting protein-based deposit accumulation, oxidative stress, and neuroinflammation, and correcting defects of neurotransmitters such as acetylcholine and dopamine [1-3]. The current review is an attempt to highlight the neuroprotective effects of medicinal plants.

2. Plants with neuroprotective activity

2.1. Bellis perennis

The effect of *Bellis perennis* was investigated on viability of healthy neuronal cell line. On treatment with 90% alcohol, the cell viability was significantly decreased to 18% as compared to the negative control (only media) which was taken as 100%. The effect of alcohol was neutralized by *Bellis perennis* at 2µl/ml, 4µl/ml and 8µl/ml. It significantly increased the cell viability [4-5].

2.2. Calendula officinalis

The neuroprotective effect of *Calendula officinalis* Linn. flower extract (COE) on Monosodium glutamate (MSG)-induced neurotoxicity was evaluated in rats. Adult Wistar rats were administered systemically for 7 days with MSG and after 1h of MSG injection, rats were treated with COE (100 and 200 mg/kg) orally. At the end the treatment period, animals were assessed for locomotor activity and were sacrificed; brains were isolated for estimation of LPO, GSH, CAT, TT, GST, Nitrite and for histopathological studies. MSG caused a significant alteration in animal behavior, oxidative defense (raised levels of LPO, nitrite concentration, depletion of antioxidant levels) and hippocampal neuronal histology.

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Treatment with COE significantly attenuated behavioral alterations, oxidative stress, and hippocampal damage in MSG-treated animals [6-7].

The neuroprotective effect of *Calendula officinalis* flower extract (COE) on 3-NP-induced neurotoxicity in rats was evaluated by observing behavioral changes, oxidative stress and striatal damage in rat brain. Adult female Wistar rats were pretreated with vehicle or COE (100 and 200 mg/kg) for 7 days, followed by cotreatment with 3-NP (15 mg/kg, intraperitoneally) for the next 7 days. At the end of the treatment schedule, rats were evaluated for alterations in sensory motor functions and short-term memory. Animals were sacrificed and brain homogenates were used for the estimation of lipid peroxidation (LPO), glutathione, total thiols, glutathione S-transferase, catalase and nitrite. A set of brain slices was used for the evaluation of neuronal damage in the striatal region of the brain. 3-NP caused significant alterations in animal behavior, oxidative defense system evidenced by raised levels of LPO and nitrite concentration, and depletion of antioxidant levels. It also produced a loss of neuronal cells in the striatal region. Treatment with COE significantly attenuated behavioral alterations, oxidative damage and striatal neuronal loss in 3-NP-treated animals [8].

2.3. Carthamus tinctorius

The neuroprotective properties of Hydroxysafflor yellow A (HSYA) on neurotoxicity of glutamate in primary cultured rat cortical neurons along with its possible mechanism of action were examined. The excitotoxic neuronal death was attenuated markedly by HSYA treatment. HSYA decreased expression of Bax and rescued the balance of pro-and anti-apoptotic proteins. In addition, HSYA significantly reversed up-regulation of NR2B-containing NMDA receptors by exposure to NMDA, while it did not affect the expression of NR2A-containing NMDA receptors [9].

The neuroprotective efficacy of the combination of (Astragali, *Ligusticum wallichii*, *Angelica sinensis* and *Carthamus tinctorius*) on mitigating brain infarction and global ischemia as well as preventing the neurodegeneration following ischemia was studied. They improved cerebral blood circulation, which refer to a potential to alleviate the symptoms of degenerative diseases, Alzheimer's disease and Parkinson's disease [10].

The neuroprotective effects of hydroxysafflor yellow A (HSYA) on cerebral ischemic injury in both *in vivo* and *in vitro* were studies. In *in vivo* experiment, male Wistar-Kyoto (WKY) rats with middle cerebral artery occlusion (MCAO) were evaluated for neurological deficit scores followed by the treatment with a single dose of HSYA. Furthermore, the infarction area of the brain was assessed in the brain slices. In *in vitro* experiment, the effect of HSYA was tested in cultured fetal cortical cells exposed to glutamate and sodium cyanide (NaCN) to identify its neuroprotection against neurons damage. The results of *in vivo* study showed that sublingular vein injection of HSYA at doses of 3.0 mg/kg and 6.0 mg/kg exerted significant neuroprotective effects on rats with focal cerebral ischemic injury by significantly decreasing neurological deficit scores and reducing the infarct area compared with the saline group, HSYA at a dose of 6.0 mg/kg, gave a similar potency as nimodipine at a dose of 0.2 mg/kg. Sublingular vein injection of HSYA at the dose of 1.5 mg/kg showed a neuroprotective effect, however, with no significant difference when compared with the saline group. *In vitro* results showed that HSYA significantly inhibited neuron damage induced by exposure to glutamate and sodium cyanide (NaCN) in cultured fetal cortical cells, however, the neuroprotective action of HSYA on glutamate-mediated neuron injury was much better than that of HSYA on NaCN-induced neuron damage [11].

Free radical scavenging activity of the extracts of petals (bud, early stage, full blooming and ending stage), leaf, stem, root and seeds of Mogami-benibana (*Carthamustinctorius*), the contents of the major active components of carthamin and polyphenols, and neuroprotective effect of the petal extracts and carthamin in the brain of mice and rats were examined. Water extracts of Mogami-benibana petals scavenged superoxide, hydroxyl and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and singlet oxygen. There was also a relationship between DPPH radical scavenging activity and carthamin content in the petal extracts of safflower [12].

The potential protective effect of Hydroxysafflor Yellow A (HSYA) in spinal cord ischemia/ reperfusion (I/R) injury was studied in rabbits. Neurological outcomes in HSYA group were slightly improved compared with those in I/R group. Histopathological analysis revealed that HSYA treatment attenuated I/R induced necrosis in spinal cords. Similarly, alleviated oxidative stress was indicated by decreased malondialdehyde (MDA) level and increased superoxide dismutase (SOD) activity after HSYA treatment. Moreover, HSYA also protected neurons from I/R-induced apoptosis in rabbits as seen from TUNEL results [13].

The probable attenuating effect of Hydroxysafflor yellow A (HSYA) on brain injury induced by lymphostatic encephalopathy (LE) was investigated in rats. Heart rate variability (HRV) was used as an indirect measurement of the regulatory function of the autonomic nervous system by recording the ECG signals from rats. It was shown that treatment with HSYA (5 mg/kg, ip) significantly alleviated the neurological deficits observed in rats with LE. Histological

staining revealed that HSYA treatment attenuated LE-induced cell apoptosis in the rostral ventrolateral medullus (RVLM). Animals in the LE groups exhibited impaired regulatory roles of the autonomic nervous system in cardiovascular function, which was suppressed by pretreatment with HSYA. Additionally, HSYA administration significantly prevented the decrease of endothelial nitric oxide synthase (eNOS) mRNA and protein expression in the RVLM of rats with LE. Accordingly, HSYA might provide neuroprotection against LE-induced brain injury and the associated functional alterations, which is likely regulated by the nitric oxide pathway [14].

The therapeutic effects of hydroxysafflor yellow A (HSYA) on focal cerebral ischemic injury in rats and its related mechanisms have been investigated. Focal cerebral ischemia in rats were made by inserting a monofilament suture into internal carotid artery to block the origin of the middle cerebral artery and administrated by HSYA via sublingular vein injection in doses of 1.5, 3.0, 6.0 mg /kg at 30 min after the onset of ischemia, in comparison with the potency of nimodipine at a dose of 0.2 mg/kg. Then, 24 h later, the evaluation for neurological deficit scores of the rats were recorded and postmortem infarct areas were determined. HSYA dose-dependently improved the neurological deficit scores and reduced the cerebral infarct area, and HSYA bore a similarity in potency of the therapeutic effects on focal cerebral ischemia to nimodipine. The inhibition rates of thrombosis formation by HSYA at the designated doses were 20.3%, 43.6% and 54.2%, respectively, compared with saline-treated group. Inhibitory activities of HSYA were observed on ADP-induced platelets aggregation in a dose-dependent manner, and the maximum inhibiton of aggregation of HSYA was 41.8%. HSYA provided a suppressive effect on production of TXA2 without significant effect on plasma PGI2 concentrations. Blood rheological parameters were markedly improved by HSYA, such as whole blood viscosity, plasma viscosity, deformability and aggregation of erythrocyte, but no significant effect for HSYA on homatocrit was found [15].

The effects of *Carthamus tinctorius* was evaluated on bcl-2, caspase-3 expression of apoptosis of neurons. The middle cerebral artery of rats was occluded for 2h by inserting an intraluminal molofilament, and reperfusion was then instituted for 4h or 22h. All treated groups at different times decreased the volume of infarction ($P<0.05$), while large-dose group showed more distinct decrease than other groups ($P<0.05$). All treated groups at different times increased bcl-2 and decreased caspase-3 expression as well, while, large-dose group showed more distinct effect ($P<0.05$) [16].

The effect of Hydroxysafflor yellow A (HSYA) on mitochondrial permeability transition pores (mtPTP) was studied in the rat brain. HSYA at 10-80 micromol/l inhibited Ca2+- and H_2O_2-induced swelling of mitochondria isolated from rat brains. The addition of Ca^{2+} generated reactive oxygen species (ROS) in isolated mitochondria, the effect which inhibited by HSYA (10-80 micromol/l). At the same time, HSYA significantly improved mitochondrial energy metabolism, enhanced ATP levels and the respiratory control ratio [17-18].

2.4. Cassia occidentalis

The antianxiety and antidepressant activity of the ethanolic and aqueous extracts of *Cassia occidentalis* leaves (500 mg/kg, orally) was evaluated in rodents. Antianxiety activity was tested by exposing rats to unfamiliar aversion in different methods like elevated plus maze model and actophotometer. In elevated plus-maze test, the ethanolic and aqueous extracts of *Cassia occidentalis* leaves at a dose of 500 mg/kg orally, significantly increased the number of entries and time spent into the open arm. The magnitude of the antianxiety effects 500 mg/kg orally, of ethanolic and aqueous extracts of *Cassia occidentalis* was comparable to that of diazepam 5 mg/kg ip. The average of basal activity scores after 30 and 60 min of administration of ethanolic and aqueous extracts of *Cassia occidentalis* leaves 500 mg/kg orally, showed significant reduction of the locomotor activity. The antidepressant activity was tested by using despair swim test and tail suspension test. In despair swim test apparatus, the ethanolic and aqueous extracts of leaves of *Cassia occidentalis* at a dose of 500 mg/kg orally, significantly decreased the immobility time. The magnitude of the antidepressant effects of 500 mg/kg orally, of ethanolic and aqueous extracts of leaves of *Cassia occidentalis* was comparable to that of fluoxetine 10 mg/kg ip. In tail suspension test, the ethanolic and aqueous extracts of leaves of *Cassia occidentalis* at a dose of 500 mg/kg orally, significantly decreased the immobility time. The magnitude of the antidepressant effects of 500 mg/kg orally, of ethanolic and aqueous leaves of *Cassia occidentalis* was comparable to that of fluoxetine 10 mg/kg ip. Ethanolic extract of *Cassia occidentalis* leaves showing more significant antidepressant activity over the aqueous extract [19-20].

Geriforte, a combination of several plant ingredients (including *Cassia occidentalis*) isbeing usedin India as a restorative tonic in old age. This preparation was evaluated for anti-stress (adaptogenic) activity by inducing various stressful situations in animals. The survival time of swimming mice increased with different doses of Geriforte. The drug also prevented changes in adrenals (increase in weight and reduction of ascorbic acid and cortisol contents) induced by stress (5 hr swimming). Both restrain and chemically-induced ulcers were prevented by 100 mg/kg of Geriforte. Furthermore, pretreatment with Geriforte prevented the increase of liver weight and volume induced by carbon tetrachloride and also the milk-induced leucocytosis. Gradual and constant increase in body weight was observed in the

rats taking the drug. However, no effect was observed on spontaneous motor activity and body temperature. It has some central nervous system stimulant activity as judged by the reduction of hexobarbital sleeping time. The LD50 as determined in acute toxicity studies on mice was between 5-6 g/kg orally [21].

2.5. Coriandrum sativum

The neuroprotective effect of *Coriandrum sativum* was evaluated against ischemic-reperfusion insult in brain. The global cerebral ischemia in albino rats was induced by blocking common carotid arteries for 30 mins followed by 45 mins of reperfusion. At the end of reperfusion period, histological changes, levels of lipid peroxidation, superoxide dismutase, catalase, glutathion, calcium and total protein were measured. Bilateral common carotid artery occlusion produced significant elevation in lipid peroxidation, calcium levels and infarct size, and decrease in endogenous antioxidants such as reduced glutathion, superoxide dismutase and catalase levels. Pretreatment with methanolic extract of leaves of *Coriandrum sativum* (200 mg/kg, po) for 15 days increased endogenous enzyme levels of superoxide dismutase, glutathion, catalase and total protein levels, and reduces cerebral infarct size, lipid peroxidation and calcium levels. It also attenuated reactive changes in brain histology like gliosis, lymphocytic infilteration and cellular edema. Accordingly, *Coriandrum sativum* possessed protective effect in ischemic-reperfusion injury and cerebrovascular insufficiency states [22].

The neuroprotective effect of *Coriandrum sativum*against glucose/serum deprivation (GSD)-induced cytotoxicity was studied *in vitro*. The PC12 cells were cultivated for 24 h in standard media (high-glucose DMEM containing Fetal Bovine Serum) or for 6 h in GSD condition (glucose-free DMEM, without serum) in the absence or presence of various concentrations (0.1, 0.2, 0.4, 0.8 and 1.6 mg/ml) of hydroalcoholic extract (HAE), water fraction (WF), ethyl acetate fraction (EAF) or N-butanol fraction (NBF) of *Coriandrum sativum*. At the end of the treatments, the cell viability was determined using MTT assay. With the exception of 1.6 mg/ml of EAF or NBF which decreased cell survival, the HAE and its fractions exhibited no cytotoxicity under standard condition. Exposure of the cells to GSD condition showed 52% decrease in the viability. Accordingly, the HAE, EAF and NBF not only failed to increase cell viability but also increased the toxicity. On the other hand, WF at 0.4, 0.8 and 1.6 mg/ml significantly attenuated the GSD-induced decrease in cell survival. The study revealed that *Coriandrum sativum* bearing water-soluble compound(s) could induce neuroprotective activity, while, some constituents from this plant may serve as cytotoxic agents under stressful conditions like hypoglycemia [24].

2.6. Crocus sativus

The protective effect of aqueous saffron extracton neurotoxicity induced by aluminuim chloride ($AlCl_3$) was evaluated in mice. Balb/c and C57BL/6 micewere injected with $AlCl_3$, 40 mg/kg/day for 45 days. Each mice strain was divided into four groups: $AlCl_3$ treated group, $AlCl_3$ plus water saffron extract group (administered with saffron extract at 200 mg/kg bw once a day for 45 days, $AlCl_3$ plus honey syrup group (administered with honey syrup at 500 mg/kg bw for 45 days). The control group received no treatment. Oxidative stress and antioxidant status were estimated in the brain and differential display was performed for both mice strains to scan the mRNA in the treated and non treated groups. In addition, the up and down regulated genes were isolated, cloned and sequenced. The sequence analysis was performed and compared with the other genes cited on GenBank. The results showed that there was a decrease in the activity of the antioxidant enzymes ($p \leq 0.001$) such as superoxide dismutase, catalase, and glutathione peroxidase in the $AlCl_3$groups of both mice strains. The level of brain thiobarbituric acid reactive substances showed a significant increase ($p \leq 0.001$) of lipid peroxidation in the $AlCl_3$ groups. There was an indication of carcinogenicity in the $AlCl_3$ treated group representing an increase in serum tumor markers such as arginase and a-l-fucosidase. More than 350 band patterns were obtained and about 22 different up-down regulated genes were observed. The sequence analysis of the three selected up-regulated genes revealed that they were similar to B-cell lymphoma 2 (Bcl-2), R-spondin and the inositol polyphosphate 4-phosphatase genes (INPP4B), respectively. The R-spondin gene was up-regulated in all examined animals except the control ones but the other two genes were only induced in the animals treated with $AlCl_3$ and honey syrup. The authors concluded that the biochemical and molecular studies revealed the neurotoxicity of $AlCl_3$ in the brains of mice. In addition, there was an ameliorative change with saffron extract and honey syrup against $AlCl_3$neurotoxicity. The obtained molecular results suggested that $AlCl_3$ made induction for BCL-W gene, which was an anticancer gene or belonged to the DNA repair system in the brain cells, as well as for R-spondin and inositol polyphosphate 4-phosphatase genes, which helped in cell proliferation [25-26].

The possible reversal effects of saffron against established aluminum (Al)-toxicitywas investigated in adult mice. Groups used includedControl, Al-treated (50 mg $AlCl_3$/kg/day diluted in the drinking water for 5 weeks) and Al+saffron (Al-treatment +60 mg saffron extract/kg/day intraperitoneally for the last 6 days). Learning/ memory, the activity of acetylcholinesterase [AChE, salt-(SS)/detergent-soluble(DS) isoforms], butyrylcholinesterase (BuChE, SS/DS isoforms), monoamine oxidase (MAO-A, MAO-B), the levels of lipid peroxidation (MDA) and reduced glutathione (GSH), in whole

brain and cerebellum were assessted. Brain Al and crocetin, the main active metabolite of saffron, were determined in brain after intraperitoneal saffron administration by HPLC. Alcaused memory impairment, significant decrease of AChE and BuChE activity, activation of brain MAO isoforms but inhibition of cerebellar MAO-B, significant elevation of brain MDA and significant reduction of GSH content. Although saffron extract co-administration had no effect on cognitive performance of mice, it reversed significantly the Al-induced changes in MAO activity and the levels of MDA and GSH. AChE activity was further significantly decreased in cerebral tissues of Al+saffron group. The biochemical changes support the neuroprotective potential of saffron under toxicity [27].

The effect of ethanol extract of *Crocus sativus* was evaluatedin the treatment of experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice. EAE was induced by immunization of 8 week old mice with MOG(35-55) with complete Freunds adjuvant. Therapy with saffron was started on the day of immunization. After daily oral dosage the saffron significantly reduced the clinical symptoms in C57BL/6 mice with EAE. Also, treated mice displayed a delayed disease onset compared with control mice. Total antioxidant capacity (TAC) production was significantly elevated in saffron treated mice. Effect of saffron on serum NO production was not significant. Typical spinal cord leukocyte infiltration was observed in control mice compared with saffron treated mice. The results suggested that saffron was effective in the prevention of symptomatic EAE by inhibition of oxidative stress and leukocyte infiltration to central nervous system (CNS) and may be potentially useful for the treatment of multiple sclerosis (MS) [28].

The neuroprotective effect of saffron extract, its active component crocin and gamma-glutamyl cysteinyl glycine (GSH) was studied in glucose-induced neurotoxicity, using PC12 cells as a suitable *in vitro* model of diabetic neuropathy. Cell viability was determined by MTT assay. ROS was measured using DCF-DA by flow cytometry analysis. The result showed that glucose (13.5 and 27 mg/ml) reduced theviability of PC12 cells after 4 days. Saffron extract(5 and 25 mg/ml), crocin (10 and 50 muM) and GSH (10 muM) decreased this toxicity. Glucose toxicity was associated withincreased ROS production which reduced by saffron, crocin and GSH pretreatment. The results suggested thatsaffron and its carotenoid crocin could be potentially useful in diabetic neuropathy treatment [29].

The preventive effectof the aqueous extract of saffron was studied againstdiazinon (DZN) -induced rise of several specific inflammation, oxidative stress and neuronal damage in rats.The saffron extract inhibited the effect of DZN on these biomarkers levels [30].

The modifying effects of*Crocus sativus* (CS) stigma extract on neurobehavioral activities, malondialdehyde (MDA), reduced glutathione (GSH), glutathione peroxidase, glutathione reductase, glutathione S-transferase, superoxide dismutase (SOD), catalase (CAT), and Na^+,K^+-ATPase activities, and glutamate (Glu) and aspartate (Asp) content were examined in the middle cerebral artery (MCA) occlusion (MCAO) model of acute cerebral ischemia in rats. The right MCA of male Wistar rats was occluded for 2 hours using intraluminal 4-0 monofilament, and reperfusion was allowed for 22 hours. MCAO caused significant depletion in the contents of GSH and its dependent enzymes, with significant elevation of MDA, Glu, and Asp. The activities of Na^+,K^+-ATPase, SOD, and CAT were decreased significantly by MCAO. The neurobehavioral activities (grip strength, spontaneous motor activity, and motor coordination) were also decreased significantly in the MCAO group. All the alterations induced by ischemia were significantly attenuated by pretreatment with CS (100 mg/kg of body weight, po) 7 days before the induction of MCAO and correlated well with histopathology by decreasing the neuronal cell death following MCAO and reperfusion [31].

A rat model of chronic cerebral hypoperfusion was used to determine the effect of saffron extract and crocin on vascular cognitive impairment. Male adult Wistar rats were administered different doses of an aqueous solution of crocin or hydroalcohol extract of saffron intraperitoneally (ip), 5 days after permanent occlusion of the common carotid arteries. Spatial learning and memory were assessed in training trials, 7-11 days after common carotid artery ligation using the Morris water maze. The results showed that the escape latency time was significantly reduced from 24.64s in the control group to 8.77 and 10.47s by crocin (25 mg/kg) and saffron extract (250 mg/kg). The traveled distance to find the platform was also changed from 772 cm in the control group to 251 and 294 cm in the crocin (25 mg/kg) and saffron extract (250 mg/kg) groups. The percentages of time spent in the target quadrant, in comparison with the control group (24.16%), was increased to 34.25% in the crocin (25 mg/kg) and 34.85% in the saffron extract (250 mg/kg) group. Accordingly, saffron extract and crocin improved spatial cognitive abilities following chronic cerebral hypoperfusion, the effect which may be related to the antioxidant effects of these compounds [32].

The ameliorative effect of saffron aqueous extract on hyperglycemia, hyperlipidemia, and oxidative stress was studied in diabetic encephalopathy in streptozotocin induced diabetes mellitus in rats. Saffron at 40 and 80 mg/kg significantly increased body weight and serum TNF-α and decreased blood glucose levels, glycosylated serum proteins, and serum advanced glycation end products (AGEs) levels. Furthermore, significant increase in HDL and decrease ($P<0.05$) in cholesterol, triglyceride, and LDL were observed after 28 days of treatment. At the end of experiments, the hippocampus

tissue was used for determination of glutathione content (GSH), superoxide dismutase (SOD), and catalase (CAT) activities. Saffron significantly increased GSH, SOD, and CAT in the the hippocampus tissue, but remarkably decreased cognitive deficit, serum TNF-α, and induced nitric oxide synthase (iNOS) activity in hippocampus tissue. Accordinglysaffron extract reduced hyperglycemia and hyperlipidemia risk and also reduced the oxidative stress in diabetic encephalopathy rats [33].

2.7. Cyperus rotundus

The neuroprotective effects of a water extract of *Cyperus rotundus* rhizoma against 6-hydroxydopamine (6-OHDA)-induced neuronal damage were evaluated in an experimental model of Parkinsons disease. In PC12 cells, water extract of *Cyperus rotundus* rhizoma showed a significant protective effect on cell viability at 50 and 100 microg/ml. Water extract of *Cyperus rotundus* rhizoma inhibited generation of reactive oxygen species and nitric oxide, reduction of mitochondrial membrane potential, and caspase-3 activity, which were induced by 6-OHDA. Water extract of*Cyperus rotundus* rhizoma also showed a significant protective effect against damage to dopaminergic neurons in primary mesencephalic culture [34-35].

The possible neuroprotective effects of the ethanol extract of *Cyperus rotundus* on a model of global transient ischemia in rat was investigated by evaluating the pathophysiology of the hippocampal tissue and spatial memory. The group treated with the ethanol extract of *Cyperus rotundus* (100 mg/kg/day) was gavaged from 4 days before, to 3 days after ischemia. Morris water maze test was performed 1 week after ischemia for 4 days. Brain tissue was prepared for Nissl staining. Data showed no statistical difference between the treatment and ischemia groups in water maze task. So, treatment of ischemia with the ethanol extract of *Cyperus rotundus* cannot improve spatial learning and memory. On the contrary the ethanol extract of *Cyperus rotundus* ameliorated the CA1 pyramidal cell loss due to transient global ischemia/reperfusion injury [36].

The neuroprotective effect of total oligomeric flavonoids (TOFs), prepared from *Cyperus rotundus*, was studied in rat model of cerebral ischemia and reperfusion. Male Sprague Dawley rats were subjected to middle cerebral artery occlusion (MCAO) for 2h and reperfusion for 70h. Experimental animals were divided into four groups: Group I - sham operated; Group II - vehicle treated ischemic-reperfusion (IR), and Group III and IV - TOFs treated (100 and 200mg/kg body weight, po, respectively). Vehicle or TOFs were pretreated for four days before the induction of ischemia and continued for next three days after the ischemia i.e. treatment was scheduled totally for a period of 7 days. MCAO surgery was performed on day 4, 1h after TOFs administration. Neuroprotective effect of TOFs was substantiated in terms of neurological deficits, excitotoxicity (glutamate, glutamine synthetase and Na^+-K^+ -ATPase levels), oxidative stress (malondialdehyde, super oxide dismutase, and glutathione) and neurobehavioral functions in the experimental animals. TOFs decreased glutamate, glutamine synthetase (GS) and increased Na^+-K^+ -ATPase activity in a dose dependent manner when compared to the IR rats. Treatment with TOFs significantly reduced the neurological deficits and reversed the anxiogenic behavior in rats. Furthermore, it also significantly decreased MDA and increased superoxide dismutase (SOD) and glutathione content in brains of experimental rats. Histopathological examination using cresyl violet staining revealed the attenuation of neuronal loss by TOFs in stroke rats [37].

The protective effect of 200 and 400 mg/kg of ethanol extract of *Cyperus rotundus* against sodium nitrite-induced hypoxia injury in rats was evaluated by assessing the cognitive functions, motor, and behavioral effects of ethanol extract of *Cyperus rotundus* treatment along with the histological changes in the brain. Ethanol extract of *Cyperus rotundus* at doses of 200 and 400 mg/kg was able to protect against the cognitive impairments, and the locomotor activity and muscular coordination defects, which were affected by sodium nitrite-induced hypoxia injury in rats [38].

The protective effects of *Cyperus rotundus* rhizome extract were evaluated through its oxido-nitrosative and anti apoptotic mechanism to attenuate peroxynitrite ($ONOO^-$) induced neurotoxicity, using human neuroblastoma SH-SY5Y cells. The results elucidate that pre-treatment of neurons with *Cyperus rotundus* rhizome extract ameliorated the mitochondrial and plasma membrane damage induced by 500 μM SIN-1 to 80% and 24% as evidenced by MTT and LDH assays. CRE inhibited NO generation by down-regulating i-NOS expression. SIN-1 induced depletion of antioxidant enzyme status was also replenished by *Cyperus rotundus* rhizome extractwhich was confirmed by immunoblot analysis of SOD and CAT. The *Cyperus rotundus* rhizome extract pre-treatment efficiently potentiated the SIN-1 induced apoptotic biomarkers such as bcl-2 and caspase-3 which orchestrate the proteolytic damage of the cell. The $ONOO^-$ induced damage to cellular, nuclear and mitochondrial integrity was also restored by *Cyperus rotundus* rhizome extract. Furthermore, *Cyperus rotundus* rhizome extract pre-treatment also regulated the 3-NT formation which revealed the potential of plant extract against tyrosine nitration [39].

2.8. Dalbergia sissoo

The neuroprotective effects of the ethanolic extract of *Dalbergia sissoo* leaves was evaluated by checking brain weight, antioxidant levels, histopathological and TTC staining studies in cerebral ischemia induced rats. The extracts (ethanolic 300, 600 mg/kg) were compared to negative control (global cerebral ischemic rats). It is observed that prior treatment of *Dalbergia sissoo* extract (DSE) (300mg/kg and 600mg/kg, po for 10days) markedly reversed the brain weight, antioxidant levels and restored to normal levels as compared to ischemia- reperfusion induced oxidative stress groups. Moreover, brain coronal sections staining and histopathological studies revealed protection against ischemic brain damage in the extract treated groups [40-41].

The neuroprotective effect of ethanolic extract of *Dalbergia sissoo* leaves was evaluated in 3-Nitropropionic acid induced neurotoxic rats. The ethanolic extract of *Dalbergia sissoo* leaves was administered orally at different doses (300 and 600 mg/kg) to neurotoxic rats. During treatment psychopharmacological parameters were recorded, 24 hours after experiment antioxidant profiles from brain isolates were estimated and histopathology of brain was performed. The ethanolic extract significantly attenuated behavioral alterations, oxidative damage, mitochondrial dysfunction, and striatal/hippocampus damage in 3-Nitropropionic acid treated rats [42].

2.9. Geum urbanum

The extracts from three Romanian medicinal plants (*E. planum, G. urbanum, and C. benedictus*) were investigated for their possible neuroprotective potential. The in vitro neuroprotective activity of the extracts were investigated via inhibition of acetylcholinesterase and tyrosinase. AChE inhibitory activities of *Geumu rbanum* 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} was 2.293±0.14 mg/ml, while AChE inhibitory activities of *Geum urbanum* ethanol extract were 54.74±2.7, 73.53±5.1 and86.77±5.1 respectively and IC_{50}mg/ml was0.513±0.03. All the concentration of aqueous and ethanol extracts (0.75 mg/ml, 1.5 mg/mland 3 mg/ml) inhibited tyrosinase more than 50%, ethanolic extract was more potent tyrosinase inhibitor than aqueous [43-44].

2.10. Hyoscymusniger

The neuroprotective potential, of petroleum ether and aqueous methanol extracts of *Hyoscyamusniger* seedswas evaluated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson diseasein mice. Parkinsonian mice were treated twice daily with the extracts (125–500 mg/kg, po.) for two days and motor functions and striatal dopamine levels were assayed. Administration of the aqueous methanol extract (containing 0.03% w/w of L-DOPA), but not petroleum ether extract, significantly attenuated motor disabilities (akinesia, catalepsy and reduced swim score) and striatal dopamine loss in MPTP treated mice. The extract caused significant inhibition of monoamine oxidase activity and attenuated 1-methyl-4-phenyl pyridinium (MPP^+)-induced hydroxyl radical (OH) generation in isolated mitochondria, Accordingly, the protective effect of the methanolic extract of *Hyoscyamus niger* seeds against parkinsonism in mice could be attributed to its ability to inhibit increased ·OH generated in the mitochondria [45-46].

The neuroprotective potential of methanol extract of *Hyoscymus niger* (MHN) seeds was investigated in stereotaxically induced rotenone model of Parkinson's disease in rats. Rats were pretreated with MHN (125, 250, 500 mg/kg body weight po) once daily for 7 days and subjected to unilateral intrastriatal injection of rotenone (8 µg in 0.1 % ascorbic acid in normal saline). Three weeks after rotenone infusion, rats were tested for neurobehavioral activity and were sacrificed for estimation of lipid peroxidation (TBARS), total glutathione (GSH) content, and activity of antioxidant enzymes glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) in brain homogenates. Administration of the MHN (containing L-DOPA) significantly attenuated motor disabilities (actophotometer, rota rod and Morris water maze test). Rat treated with rotenone showed reduced levels of thiobarbituric acid reactive substance (TBARS) and increased level of GSH content and antioxidants enzymes activities (GPX, SOD and CAT) in the MHN treated PD rat. The extract showed presence of L-dopa with significant inhibition in DPPH, ABTS in-vitro assay and monoamine oxidase activity [47].

2.11. Juglans regia

The neuroprotective effect of dietary walnut (6%) against cisplatin-induced neurotoxicity was investigated in rats. dietary walnut (6%) through studying the alteration in performance of hippocampus- and cerebellum-related behaviors following chronic cisplatin treatment (5 mg/kg/week for 5 consecutive weeks) in male rats. The exposure of rats to cisplatin resulted in significant decrease in explorative behaviors and memory retention. Walnut consumption improved memory and motor abilities in cisplatin treated rats, while walnut alone did not show any significant changes in these abilities compared to saline. Cisplatin increased latency of response to nociception, and walnut reversed this effect of cisplatin [48-49].

The neuroprotective efficacy of dietary supplementation of walnut (6 %) for 28 days was examined in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (20 mg/kg bw/day, ip) for last four consecutive days. MPTP injection diminished the levels of GSH, dopamine and metabolites along with decreased activities of GPx and mitochondrial complex I. The levels of TBARS and enzymatic antioxidants such as SOD and catalase, MAO-B activities were enhanced by MPTP treatment. Behavioral deficits and lowered TH expression were also proved inMPTP induced neurotoxicity. Dietary supplementation of walnut attenuated MPTP-induced impairment in PD mice could be attributed to its MAO-B inhibitory, antioxidant and mitochondrial protective actions [50].

Walnuts, rich in polyphenols, antioxidants, and omega fatty acids such as alpha-linolenic acid and linoleic acid, improved the age-associated declines in cognition and neural function in rats. Possible mechanisms of action of these effects include enhancing protective signaling, altering membrane microstructures, decreasing inflammation, and preventing accumulation of polyubiquitinated protein aggregates in critical regions of the brain. The serum collected from aged animals fed with walnut diets (0, 6, and 9%, w/w) enhanced protection on stressed BV-2 microglia in vitro. Walnut significant reduced pro-inflammatory tumor necrosis factor-alpha, cyclooxygenase-2, and inducible nitric oxide synthase. These results suggested antioxidant and anti-inflammatory protection or enhancement of membrane-associated functions in brain cells [51].

2.12. Lagerstroemia speciosa

The neuroprotective effects of alcoholic extract of *Lagerstroemia speciosa* (50 and po, for 58 days) was investigated in painful diabetic neuropathy in streptozotocine induced diabetic neuropathy in rats. Lipid peroxidation, reduced glutathione and nitric oxide content in sciatic nerve were evaluated. The extract significantly restored the reduced body weight and the elevated blood sugar level. The extract also showed dose dependent reduction in pain threshold tested by mechanical, cold and thermal hyperalgesia. The extract also showed antioxidant effects [52-53].

2.13. Lithospermum officinale

Shikonin exhibited a neuroprotective effect against the damage caused by ischemia/reperfusion in mice, it decreased the neurological deficit scores, infarct size, and levels of malondialdehyde, carbonyl, and reactive oxygen species. The neuroprotective effect of shikonin could be mediated by its antioxidant effects. The neuroprotective activity of shikonin and its derivatives was also been described in microglial cells which were the prime effectors in immune and inflammatory responses of the central nervous. Two of shikonins derivatives (isobutyryl- and isovalerylshikonin) were more effective than shikonin in repressing microglial LPS-induced activation. Shikonin also protected dopaminergic neurons against 6-hydroxydopamineinduced neurotoxicity [54-56].

2.14. Lycium barbarum

The neuroprotective effects of *Lycium barbarum* polysaccharides (LBP, 150 mg/kg or 300 mg/kg) on photoreceptor degeneration and the mechanisms involved were assessed in oxidative stress in light-exposed mouse retinas. LBP significantly improved the electroretinography (ERG) amplitudes of the α- and β-waves that had been attenuated by light exposure. Furthermore, the changes caused by light exposure including photoreceptor cell loss, nuclear condensation, an increased number of mitochondria vacuoles, outer membrane disc swelling and cristae fractures were distinctly ameliorated by LBP. It also significantly prevented the generation of reactive oxygen species (ROS). The levels of nuclear factor erythroid 2-related factor 2 (Nrf2) and thioredoxin reductase (TrxR1) mRNA were increased remarkably in LBP- treated mice. The mRNA levels of the DNA repair gene Poly (ADP-ribose) polymerase (PARP14) was decreased significantly in the LBP treated mice [57].

The neuroprotective effects of *Lycium barbarum* polysaccharides (LBP) on primary cultured hippocampal neurons injured by oxygen-glucose deprivation/reperfusion (OGD/RP) was studied in rats. LBP increased the cell abilities and decreased the cell

morphologic impairment. It increased MMP but inhibited Ca2+ elevation and significantly suppressed over expression of NF- κB, IL-6 TLR4 and increased IκB expression [58].

The neuroprotective effects of the alkaline extract of *Lycium barbarum* (LBB), in attenuation beta-amyloid peptide neurotoxicity were investigated. Primary cortical neurons were exposed to beta-amyloid peptide inducing apoptosis and neuronal cell death. Pretreatment of LBB significantly reduced the level of lactate dehydrogenase (LDH) release and the activity of caspase-3 triggered by beta-amyloid peptide. Three sub-fractions were isolated from alkaline extract (alkaline extract-0, alkaline extract-I and alkaline extract-II). Alkaline extract-I and alkaline extract-II showed differential neuroprotective effects [59].

The neuroprotective effects of *Lycium barbarum* polysaccharides (LBP) was studied in neurons stressed by beta-amyloid peptide. Pretreatment with LBP effectively protected neurons against beta-amyloid peptide -induced apoptosis by reducing the activity of both caspase-3 and -2, but not caspase-8 and -9. A new arabinogalactan-protein (LBP-III) was isolated from LBP and attenuated beta-amyloid peptide-activated caspase-3-like activity. LBP-III markedly reduced the phosphorylation of PKR triggered by beta-amyloid peptide, reduction of its phosphorylation triggered by beta-amyloid peptide implicated that LBP-III from Fructuslycii was a potential neuroprotective agent in Alzheimer's disease [60].

The neuroprotective effect of wolfberry (*Lycium barbarum*) was studied against homocysteine -induced neuronal damage. The results showed that polysaccharides derived from wolfberry treatment significantly attenuated homocysteine -induced neuronal cell death and apoptosis in primary cortical neurons as demonstrated by LDH and caspase-3 like activity assay. Polysaccharides also significantly reduced homocysteine- induced tau phosphorylation at tau-1 (Ser198/199/202), pS396 (Ser396), and pS214 (Ser214) epitopes as well as cleavage of tau, while, the phosphorylation level of p-GSK3*β* (Ser9/Tyr 216) remained unchanged among different treatment groups at all detected time points. Polysaccharides derived from wolfberry also suppressed elevation of both p-ERK and p-JNK [61].

The neuroprotective effects of *Lycium barbarum* water extract were studied in a differentiated (D)PC12 cellular apoptosis model induced by L-glutamic acid (L-Glu), and a mouse model of Alzheimer's disease, induced by the combination of $AlCl_3$ and D-galactose. The extract markedly increased DPC12 cell survival against L-Glu induced damage by increasing cell viability, reducing the apoptosis rate and G1 phase arrest, suppressing intracellular reactive oxygen species accumulation, blocking Ca2+ overload and preventing mitochondrial membrane potential depolarization. The extract also normalized the expression levels of apoptosis regulator Bcl-2, apoptosis regulator BAX, and cleaved caspase-3, -8 and -9 in L-Glu exposed cells. In Alzheimer's disease mouse model, the extract increased the amount of horizontal and vertical movement in the autonomic activity test, improved endurance time in the rota rod test, decreased escape latency time in the Morris water maze test, and significantly increased the levels of acetylcholine and choline in the serum and hypothalamus [62].

The neuroprotective mechanism of *Lycium barbarum* polysaccharides against chronic intermittent hypoxia induced spatial memory deficits was studied in rats. Rats were exposed to hypoxic treatment resembling a severe obstructive sleep apnea condition for a week, they fed with polysaccharides solution (1mg/kg) orally, daily 2 hours prior to hypoxia. Polysaccharides administration normalized the elevated level of oxidative stress, neuroinflammation, endoplasmic reticulum stress, autophagic flux and apoptosis induced by hypoxia. In addition, polysaccharides significantly mitigated both the caspase-dependent intrinsic (Bax, Bcl2, cytochrome C, cleaved caspase-3) and extrinsic (FADD, cleaved caspase-8, Bid) signaling apoptotic cascades. Furthermore, polysaccharides administration prevented the spatial memory deficit and enhanced the hippocampal neurogenesis induced by hypoxia [63].

The electrophysiological parameters of responses of motoneurons of the spinal cord at high-frequency stimulation of the distal part of the injured sciatic nerve was studied in a rat model of diabetic stress under action of *Lycium barbarum*. The results showed that *Lycium barbarum* fruit modulated central nervous system reorganization, amplifying positive adaptive changes that improved functional recovery and promoted selective target re-innervation in high fructose-diet rats with sciatic nerve crush injury [64].

The protective effects, and the possible mechanism of action of *Lycium barbarum* polysaccharides (LBP) against 6-hydroxydopamine (6-OHDA)-induced apoptosis was evaluated in PC12 cells. The results showed that LBP significantly reversed the 6-OHDA-induced decrease in cell viability, prevented 6-OHDAinduced changes in condensed nuclei and decreased the percentage of apoptotic cells in a dose-dependent manner. It also slowed the accumulation of reactive oxygen species and nitric oxide, decreased the level of protein-bound 3-nitrotyrosine (3-NT) and intracellular free Ca2+, and inhibited the over expression of nuclear factor κB (NF-κB), neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) [65].

The neuroprotective effect of the extracts of *Lycium barbarum* was studied against toxicity of fibrillar Abeta in rats. Rats cortical neurons exposed to Abeta peptides resulted in apoptosis and necrosis. Pre-treatment with extract of *Lycium barbarum* significantly reduced the release of lactate dehydrogenase and attenuated Abeta peptide-activated caspases-3-like activity. Pre491 treatment with an aqueous extract also markedly reduced the phosphorylation of JNK-1 (Thr183/ Tyr185) and its substrates c- Jun-I (Ser 73) and c-Jun-II (Ser 63) [66].

The effect and possible mechanisms of *Lycium* extract-mediated protection of β- amyloid -induced paralysis was studied in *Caenorhabditis elegans. Lycium* extracts effectively reduced β- amyloid accumulation and delayed β- amyloid – induced paralysis in a transgenic *C. elegans* model. It appeared that the expression of mitochondrial unfolded protein response (UPRmt), endoplasmic reticulum unfolded protein response (UPRER) and autophagy related genes was

induced by *Lycium* extracts in CL2006 transgenic strains but not in the wild-type stains. Furthermore, RNAi experiments revealed that knock down of the UPRmt-related genes could reduce levels of down-regulation induced by *Lycium* extracts, suggesting that UPRmt was necessary for *Lycium* to prevent β- amyloid aggregation and maintain protein stabilization [67].

The neuroprotective effect of *Lycium barbarum* polysaccharides (LBP) was evaluated in mice model of cerebral artery occlusion/reperfusion (MCAO/R). LBP at doses of 20 and 40 mg/kg markedly decreased the neurological deficit scores and the infarction area in MCAO/R mice. LBP also significantly decreased MDA content, and increased SOD, GSH-Px, CAT, LDH activities in ischemic reperfusion brain [68].

The neuroprotective effect of *Lycium barbarum* polysaccharide (LBP) on focal cerebral ischemic injury was studied in mice. LBP (10, 20 and 40 mg/kg) treatment significantly reduced infract volume and neurological deficit scores, it also relieved neuronal morphological damage and attenuated the neuronal apoptosis. LBP at the dose of 40 mg/kg significantly suppressed over expression of Bax, CytC, Caspase-3, -9 and cleaved PARP-1, and inhibited the reduction of Bcl-2 expression [69].

The ameliorating effect of polysaccharides of *Lycium barbarum* (LBP) was studied in hyperglycemia-aggravated ischemia/reperfusion brain injury in rats. In hyperglycemic group, increased neurological deficits, infarct volume, and evidence of neuronal pyknosis at 24- and/or 72-h of reperfusion ($p< 0.05$) were recorded, and pre-treatment with LBP decreased these effects ($p< 0.05$). Immuno-histochemistry revealed an increase of Drp1 and a decrease of Opa1 positive neurons in the hyperglycemic group after 24 and 72 hours of reperfusion when compared to the normoglycemic group. LBP treatment prevented the hyperglycemia -induced alterations in Drp-1 and Opa1 expression [70].

2.15. Mangifera indica

The protective effect of *Mangifera indica* leaf extract (100, 200, 300 mg /kg bw, orally for 28 days) against cadmium-induced neurotoxicity was studied in ras. Cd increased levels of the cortical oxidative biomarkers (malondialdehyde, nitric oxide, oxidized form of glutathione, 8-hydroxy-2-deoxyguanosine) and the inflammatory mediators (TNF-α and IL-1β), while lowered glutathione content, superoxide dismutase, catalase, glutathione peroxidase and ATP levels. Also, Cd significantly decreased the AChE activity and the tested biogenic amines while elevated the tested metabolites in the frontal cortex. Levels of all disrupted cortical parameters were alleviated by the extract coadministration. The extract induced apparent protective effect on Cd- induced neurotoxicity in concern with its medium and higher doses which may be due to its antioxidant and anti-inflammatory activities [71-72].

2.16. Matricaria chamomilla

The neuroprotective effect of ethyl alcohol extract of *Matricaria chamomilla* extract (50, 100 and 200 mg/kg, bw) on cerebral ischemia induced motor dysfunctions was studied in rats. The extract of *Matricaria chamomilla* significantly improved ischemia/ reperfusion induced motor dysfunction. It was also significantly reduced serum MDA level which elevated by ischemia/reperfusion. However, it possessed no significant effects on the total antioxidant capacity of the brain (hippocampus and cortex) and serum, and serum NO level [73].

The protective effects of a commercial eye drop (Dacriovis™) containing *Matricaria chamomilla* and *Euphrasia officinalis* extracts in corneal epithelial cells damage (HCEC-12) caused by oxidative stress and inflammation induced by UVB radiation were studied in human. HCEC-12 cells were exposed to UVB radiation and treated with the eye drops at various concentrations. Cell viability, wound healing, reactive oxygen species (ROS) levels, protein and lipid oxidative damage and COX-2, IL- 1β, iNOS, SOD-2, HO-1 and GSS gene expression, were investigated. Eye drops protected corneal epithelial cells from UVB-induced cell death and ameliorated the wound healing, it possessed a strong antioxidant activity, decreasing ROS levels and protein and lipid oxidative damage. It also possessed anti-inflammatory activities by decreasing COX-2, IL- 1β, iNOS expression, counteracted UVB-induced GSS and SOD-2 expression and restored HO-1 expression to control levels [74].

2.17. Medicago sativa

The neuroprotective effect of methanol extract of *Medicago sativa* on ischemia and reperfusion-induced cerebral injury was investigated in mice. Pre-treatment with *Medicago sativa* methanolic extract (100 or 200 mg/kg, orally) markedly reduced cerebral infarct size, xanthine oxidase, O−2 production, thiobarbituric acid-reactive substance, and significantly restored reduced glutathione, superoxide dismutase and total tissue sulfhydryl levels and attenuated impairment in short-term memory and motor coordination. The extract directly scavenged free radicals generated against a stable

radical 1,1- diphenyl-2-picrylhydrazyl and O^{-2} generated in phenazine methosulphate- nicotinamide adenine dinucleotide systems, and also inhibited XD/XO conversion and resultant O–2 production [75].

A combined molecular docking and network analysis were carried out to study the mechanisms of the beneficial effect of *Medicago sativa* in neurodegenerative diseases. *Medicago sativa* showed memory improving activities and central nervous protective effects, which attributed to its triterpenesaponins contents [76-77].

2.18. Melilotus officinalis

The protective effect of *Melilotus officinalis* extract (100, 250 and 500 mg/kg, for 3 days) on the brain tissues in acute cerebral ischemia induced by occlusion of carotid artery, was studied in rats. Cerebral ischemia was confirmed by estimation of infract volume and neurological deficit score, in addition to plasma biochemical parameters such as 6-keto-PGF1α and TXB2 and concentration of cytokine, oxidative stress, apoptosis ratio and protein expressions of Bcl2 & Bax in the brain tissues. The extract significantly ($p<0.01$) decreased the infract volume and neurological deficit score compared with negative control group. It also significantly ($p<0.01$) decreased oxidative stress and cytokine in the brain tissues and increased plasma concentration of 6-keto-PGF1α. Plasma concentration of TXB 2 was significantly enhanced by the extract. Extract was also ameliorated the apoptosis induced by cerebral ischemia [78-79].

2.19. Melissa officinalis

The neuroprotective effects of *Melissa officinalis* were investigated against neuron toxicity in hippocampal primary culture induced by 3,4- methylene dioxy methamphetamine (MDMA) or ecstasy. A high dose of ecstasy caused profound mitochondrial dysfunction, around 40% less than the control value, and increased apoptotic neuronal death to around 35% more than the control value in hippocampal neuronal culture, while, co-treatment with *Melissa officinalis* significantly reversed these damages to around 15% and 20% respectively of the MDMA alone group, and provided protection against MDMA-induced mitochondrial dysfunction and apoptosis in neurons [80].

The efficacy of aqueous extract of *Melissa officinalis* in attenuating Mn induced brain oxidative stress was studied in mice. Mn-treated mice showed a significant increase in thiobarbituric acid reactive species levels in both the hippocampus and striatum. These changes were accompanied by a decrease in total thiol content in the hippocampus and a significant increase in antioxidant enzyme activity (superoxide dismutase and catalase) in the hippocampus, striatum, cortex and cerebellum. Co-treatment with *Melissa officinalis* aqueous extract in Mn treated mice, significantly inhibited the antioxidant enzyme activities and attenuated the oxidative damage (thiobarbituric acid reactive species and decreased total thiol levels) [81].

The methanolic and aqueous extracts of *Melissa officinalis* were tested for protective effects on hydrogen peroxide induced toxicity in PC12 cells, free radical scavenging properties, inhibition of MAO-A and acetylcholinesterase enzymes and affinity to the $GABA_A$-benzodiazepine receptor were also studied. The plant showed significant ($P<0.05$) protective effect on hydrogen peroxide induced toxicity in PC12 cells. The extracts also showed good free radical scavenging activity. Both extracts inhibited MAO-A, but no activity was detected on the acetylcholinesterase and GABA [82].

The mechanism of leaves extract of *Melissa officinalis* related to neurogenesis was investigated in mice. Administered of 50 or 200 mg/kg leaves extract to mice once a day for 3 weeks, increased cell proliferation, neuroblast differentiation and integration into granule cells by decreasing serum corticosterone levels as well as by increasing GABA levels in the mouse hippocampal dentate gyrus [83].

2.20. Mentha longifolia

A remarkable acetylcholinesterase inhibitory activity of the ethyl acetate fraction of *Mentha longifolia* (IC50=12.3μg/ml) and essential oils suggested their neuroprotective property against Alzheimer's disease [84].

The neuroprotective effect of *Mentha longifolia* ethanol extract (50, 100, and 200 mg/kg/day for 21 days) on brain ischemia in stroke model was studied in rats. Pretreatment with *Mentha longifolia* ethanol extract resulted in a significant reduction in total infarct volume, brain water content and Evans Blue extravasation in the ischemic hemisphere compared with the control. *Mentha longifolia* ethanol extract (100 and 200 mg/kg/day) increased brain antioxidant capability. The antioxidant capacity of the serum in the 100 mg/kg/day group was significantly higher and the MDA level in the serum was significantly lower than that of the control group [85-86].

2.21. Momordica charantia

The neuroprotective effect of *Momordica charantia* polysaccharide (MCP) was tested against cerebral ischemia/reperfusion injury through scavenging superoxide (O2-), nitric oxide (NO) and peroxynitrite (ONOO-), in addition to inhibition of c-Jun N-terminal protein kinase (JNK3) signaling cascades. MCP dose-dependently attenuated apoptotic cell death in neural cells under OGD condition *in vitro* and reduced infarction volume in ischemic brains *in vivo*, it had direct scavenging effects and inhibited lipid peroxidation. MCP also inhibited the activations of JNK3/c-Jun/Fas-L and JNK3/cytochrome C/caspases-3 signaling cascades in ischemic brains *in vivo* [87].

Momordica charantia polysaccharide (MCP) possessed antioxidant effect in intra-cerebral hemorrhage damage, and significantly attenuating the neuronal death induced by thrombin in primary hippocampal neurons. MCP also prevented the activation of the c-Jun N-terminal protein kinase (JNK3), c-Jun and caspase-3, caused by the intra-cerebral hemorrhage. The results indicated that MCP possessed a neuroprotective effect in response to intra-cerebral hemorrhage and the inhibition of JNK3 signaling pathway was involved in its mechanism [88].

The chronic administration of *Momordica charantia* polysaccharides (MCP) (100, 200, 400 mg/kg/day) significantly prevented depressive like behaviors in chronic social defeat stress (CSDS) mice as assessed by social interaction test (SIT), sucrose preference test (SPT), and tail suspension test (TST). Elevated levels of proinflammatory cytokines, TNF-α, IL-6, IL-1β, and expression of JNK3, c-Jun, P-110β proteins were recorded in the hippocampus of CSDS mice. The activity of PI3K and phosphorylation level of AKT were reduced in the hippocampus of CSDS mice. Administration of MCP reversed these changes. The protective effects of MCP on CSDS mice were partly inhibited by the PI3K inhibitor, LY294002 [89].

2.22. Morus nigra

The antidepressant-like and neuroprotective effects of *Morus nigra* and syringic acid, were studied against glutamate-induced damage, the role of the PI3K/Akt/GSK-3β signaling pathway in antidepressant-like effects was also evaluated. Treatment with *Morus nigra* (3 mg/kg) and syringic acid (1 mg/kg) for 7 days, triggered an antidepressant-like effect, similar to fluoxetine (10 mg/kg). The treatments evoked neuroprotection against glutamatergic excitotoxicity in hippocampal slices, and also afforded protection in cerebrocortical slices. The neuroprotective effect of *Morus nigra* and syringic acid was mediated, at least in part, by PI3K/Akt/GSK- 3β signaling pathway [90].

The antidepressant-like effects, antioxidant effects, and neuroprotective effects of *Morus nigra* leaves extract and syringic acid were studied in mice model of depression induced by corticosterone. Corticosterone administered in male mice (20 mg/kg, once a day, for 21 days) induced depressive-like phenotype, accompanied by increasing of oxidative stress markers (lipid peroxidation, nitrite, and protein carbonyl), decreasing of nonprotein thiols level, and impairment in the hippocampus. The treatment with *Morus nigra* leaves extract (10 mg/kg), syringic acid (1 mg/kg), or fluoxetine (10 mg/kg), once a day for the last 7 days of the corticosterone treatment, was able to abolish the behavioral alterations elicited by corticosterone. Both treatments also exerted antioxidant property in the mice's brain, reducing the amount of oxidative stress and abolishing the corticosterone-induced damage in the hippocampal slices. Furthermore, they protected the hippocampus against the damage induced by the association between corticosterone administration and glutamate excess [91].

2.23. Myrtus communis

The neuroprotective effect of myrtle was studied against lipopolysaccharides (LPS) induced neurotoxicity in rat. Nitric oxide, malondialdehyde, interleukine-1β, tumour necrosis factor α, estrogen, 5LOX, 15LOX, lipoxin A4, asymmetric dimethyl arginine (ADMA) and Willebrand factor (VWF) were determined in serum and brain tissue of challenged rats. The results revealed significant increase in the investigated stress parameters associated with significant decrease in the estrogen level in LPS-intoxicated rats. Marked amelioration was detected in all the studied biomarkers [92].

2.24. Nerium oleander

PBI-05204, a supercritical CO_2 extract of *Nerium oleander*, exerted significant neuroprotection to neural tissues damaged by oxygen and glucose deprivation occurred in ischemic stroke. The neuroprotective activity of PBI-05204 was maintained for several hours after oxygen and glucose deprivation treatment. The neuroprotective activity of PBI-05204 was mediated through oleandrin and/or other glycoside constituents. Accordingly, the authors suggested a clinical potential for PBI-05204 in the treatment of ischemic stroke and prevention of associated neuronal death [93-94].

2.25. Nigella sativa

The effects of *Nigella sativa* in experimental spinal cord injury in rats were studied in comparison with methyl prednisolone. Both treatments decreased tissue MDA and protein carbonyl levels and prevented inhibition of SOD, GSH-Px and CAT enzymes in the tissues. The neurons in methyl prednisolone and *Nigella sativa* -treated groups were well protected [95].

The beneficial effects of *Nigella sativa* and thymoquinone on neurodegeneration in hippocampus after chronic toluene exposure were studied in rats. Chronic toluene exposure caused severe degenerative changes, shrunken cytoplasma, slightly dilated cisternae of endoplasmic reticulum, markedly swollen mitochondria with degenerated cristae and nuclear membrane breakdown with chromatin disorganization in neurons of the hippocampus. However, n neurodegenerative changes in hippocampus after chronic toluene exposure and the distorted nerve cells were absent in rats treated by *Nigella sativa* and thymoquinone [96].

Thymoquinone possessed strong protective effect against ethanol induced neuronal apoptosis in primary rat cortical neurons, it inhibited the apoptotic cascade by increasing Bcl-2 expression, repressed the activation of caspase-9 and caspase-3, reduced the cleavage of PARP-1 and prevented morphological changes [97].

The neuroprotective role of the aqueous, hydroalcoholic, chloroform and petroleum ether extracts of *Nigella sativa* seeds (400 mg/kg, orally for 7 days) were evaluated in cerebral ischemia induced by middle cerebral artery occlusion in rats. Pretreatment with *Nigella sativa* seeds extracts improved locomotor activity and grip strength of animals. Furthermore, the changes in the level of lipid peroxidation, glutathione, superoxide dismutase and catalase levels produced by middle cerebral artery occlusion were reversed [98-99].

Nigella sativa seed oil significantly reversed the abnormalities induced by propoxur in the lipid peroxidation, acetylcholine esterase activity, protein carbonyl content and possessed antioxidant activities in different parts of rat brain [100].

The neuroprotective effect of *Nigella sativa* in the hippocampus neurons exposed to global ischemia/ reperfusion was evaluated in rats. *Nigella sativa* extract prevented the ischemia/reperfusion histopathological changes in the hippocampus tissue [101].

2.26. Ocimum basilicum

The neuroprotective effect of *Ocimum basilicum* leaf extract (200 and 400 mg/kg, orally, once daily for 7 days) was studied following cerebral injury induced by bilateral common carotid artery occlusion followed by reperfusion in mice. Cognitive outcomes and sensorimotor disturbances were evaluated with Morris Water Maze, Elevated Plus Maze and neurological severity score, respectively. Treatment with the extract resulted in marked improvement in memory and motor coordination. The extract also decreased cerebral infarct size and oxidative stress in mice. The extract contained high total phenol content, and possessed strong antioxidant effects [102-103].

2.27. Oxalis corniculata

The neuroprotective effect of alcoholic extract of *Oxalis corniculata*, was evaluated via the analysis of behavioral features in MPTP (1-methyl,4- phenyl-1,2,3,6-tetra hydro pyridine) induced Parkinsonic mouse. Behavioral studies were performed by the actophotometer**,** elevated plus maze**,** rota rod, hole board, step down and step through tests. Treatment with *Oxalis corniculata* reversed the alterations in locomotor and muscle coordination in MPTP induced Parkinsonic mouse. Different doses of *Oxalis corniculata* increased memory retention and retrieval significantly. The authors concluded that the memory retention and retrieval enhancement of *Oxalis corniculata* extract could be attributed to the presence of antioxidants such as flavonoids, coumarins, tocopherols and phenolic acids [104].

3. Conclusion

The management of neurodegenerative diseases remains a challenge in the modern medicine because of their complicated pathogenesis. Many medicinal plants possessed neuroprotective effect by many mechanisms. The current review discussed the medicinal plants with neuroprotective effect.

Compliance with ethical standards

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Disclosure of conflict of interest

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