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Neuroprotective Herbal Plants - A Review

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Abstract *— The goal of neuroprotection is to shield neurons against damage, whether that damage is caused by environmental factors, pathogens, or neurodegenerative illnesses. Inhibiting protein-based deposit buildup, oxidative stress, and neuroinflammation, as well as rectifying abnormalities of neurotransmitters like dopamine and acetylcholine, are some of the ways in which medicinal herbs have neuroprotective effects [1-3]. This review will focus on the ways in which medicinal herbs may protect neurons.*

Keywords *— Neuroprotective, Medicinal plants, CNS, Neurons*

I. INTRODUCTION

The goal of neuroprotection is to shield neurones against damage, whether that damage is caused by environmental factors, pathogens, or neurodegenerative illnesses. Traditional medicine's profile has grown in recent years. Inhibiting protein-based deposit buildup, oxidative stress, and neuroinflammation, as well as rectifying abnormalities of neurotransmitters like dopamine and acetylcholine, are some of the ways in which medicinal herbs have neuroprotective effects [1-3]. The purpose of this review is to draw attention to the neuroprotective properties of medicinal herbs.

Plants with neuroprotective activity

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].

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].

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]·

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].

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-GSK3β (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 AlCl3 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].

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].

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].

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].

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].

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 GABAA-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].

Mentha longifolia

A remarkable acetylcholinesterase inhibitory activity of the ethyl acetate fraction of *Mentha longifolia* ($IC50=12.3\mu g/ml$) 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].

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].

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].

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].

Nerium oleander

PBI-05204, a supercritical CO2 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].

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].

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].

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].

II. 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.

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