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Medicinal Plants with Central Nervous Activity- An Overview (Part 1)

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Abstract: The recent studies showed that many plants affected the central nervous system and exerted many pharmacological effects including sedative, anticonvulsant, antidepressant, antipsychotic, anxiolytic, anti-Parkinson, memory-enhancing, locomotor and neuroprotective effects. The current review discuss the central nervous effects of the medicinal plants with special focus on their mode of action.

Keywords: Medicinal plants, CNS, sedative, Anticonvulsant, Antidepressant, Antiparkinson, Antipsychotic, Anxiolytic, Memory-enhancing, Locomotor, Neuroprotective.

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I. INTRODUCTION

Plants are a valuable source of a wide range of secondary metabolites, which are used for treatment and prevention of the diseases. Many medicinal plants possessed anticonvulsant, antidepressant, antianxiety, sedative, locomotor activity and memory enhancement effects. They were also showed beneficial effects in many neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, dementia, stress and fatigue.

Medicinal plants exerted antidepressant effects through synaptic regulation of serotonin, noradrenaline, and dopamine, regulating activity of hypothalamic-pituitary-adrenal axis and antioxidant effects[1]. They possessed sedative and anxiolytic effects via potentiation of the inhibitory or decreasing the excitotory neurotransmission. However, in general, the mechanisms of action of the medicinal plants used for treatment of psychiatric disorders involved modulation of neuronal communication, via specific plant metabolites binding to neurotransmitter/ neuromodulator receptors, stimulating or sedating CNS activity, and regulating or supporting the healthy function of the endocrine system[2-3]. The antiepileptic activity of medicinal plant was mediated by NMDA receptor antagonism, blocking sodium channels, decreasing Ca^{2+} influx, GABA agonistic effect, benzodiazepine agonistic activity, reducing dopamine output and interaction with and modulation of other transmitters[4]. The beneficial effects of medicinal plants in neuro degenerative disorders was mediated via their antioxidant activity, anti-excitotonic effect, apoptotic inhibition, neurotrophic effects, enhancing protective signaling, altering membrane microstructures, decreasing inflammation, and preventing accumulation of polyubiquitinated protein aggregates in critical regions of the brain[5-6]. This review will highlight the central nervous effects of the medicinal plants.

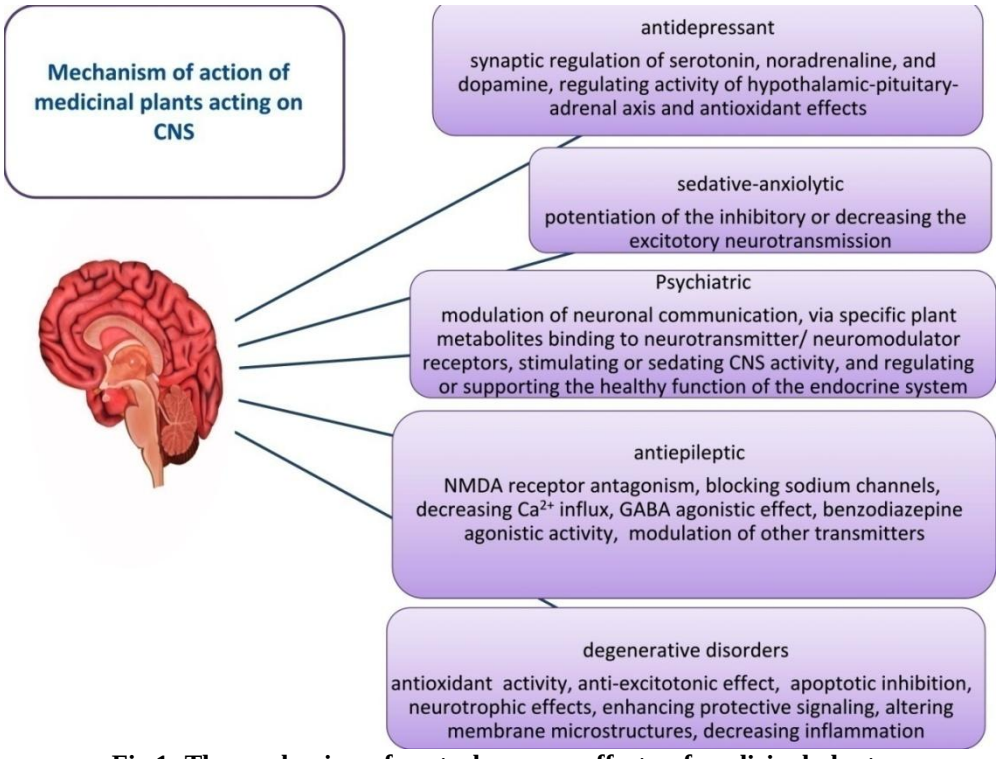

Fig 1: The mechanism of central nervous effects of medicinal plants

II. Plants with anticonvulsant effect:

Bacopa monniera

Crude plant extract of *Bacopa monnieri* or bacosides have also shown anticonvulsive action**.** It possessed neuroprotective effects in glutamate-mediated excitotoxicity during seizures and cognitive damage occurring inassociation with pilocarpine-induced epilepsy[98]. The ethanolic extract of *Bacopa monniera* was tested for anticonvulsant activity using different convulsive models (pentylenetetrazol, maximal electroshock and strychnine-induced convulsion in rats, as well as hypoxic stress-induced convulsions in mice and lithium–pilocarpine-induced status epilepticus). The ethanolic extract of *Bacopa monniera* was administered as 50 and 55 mg/kg orally for rats and mice, respectively, 2 and 4 hours before the respective convulsive stimuli. The ethanolic extract of leaves produced significant anticonvulsant activity for all the different models studied with a mechanism of action similar to that of benzodiazepines (GABA agonist)[7].

Benincasa hispida

The anticonvulsant properties of alcoholic extract of *Benincasa hispida* was studied on maximal electroshock test (MEST), pentylenetetrazole and strychnine-induced seizures model in mice. The alcoholic extract of *Benincasa hispida* protected animals against maximal electroshock-induced convulsion and reduced the mean recovery time from convulsion. It also showed anticonvulsant activity against pentylenetetrazole-induced convulsion and protected mice against strychnine-induced convulsions[8].

Brassica nigra

The antiepileptic activity of methanolic extract of *Brassica nigra* seeds was investigated on maximal electroshock induced seizures (MES), Pentylene tetrazole (PTZ), Picrotoxin (PIC) and biccuculine induced seizures in mice. It was found that the extract (200 and 400 mg/kg, orally), significantly prolonged the onset of tonic seizures and reduced the duration of incidence of seizures in PTZ, PIC and biccuculine induced seizure models, while in MES model, the extract showed significant effect in abolishing tonic hind limb extensions by inhibiting voltage dependant Na+ channels or by blocking glutaminergic excitation mediated by the N-methyl-D-aspartate (NMDA) receptor [9].

The anti-epileptic effect of the methanolic extract of *Brassica nigra* seeds (75, 150 and 300 mg/Kg; ip) was evaluated in pentylentetrazole (PTZ) - induced kindling in mice. The methanolic extract of *Brassica nigra* seed reduced the intensity and duration of seizure. In addition, the *Brassica nigra* extract increased the SOD and NO levels and decreased the MDA level in the brain tissues[10].

Bryophyllum calycinum

The CH2Cl 2/CH3OH extract reduced seizures induced by pentylenetetrazol, strychnine sulphate and thiosemicarbazide and increases in the latency period of seizures and reduced the duration of seizures induced by the three convulsive agents[11-13].

Caesalpinia crista

The anticonvulsive effect of seed extract of *Caesalpinia crista* was investigated by pentylenetetrazole, maximal electro shock strychnine- and picrotoxin-induced convulsions models. Diazepam was used as astandard reference for all models except maximal electro shock model, wherein phenytoin wasused as standard reference. Seed kernels of *Caesalpinia crista* were powdered and subjected to successive extraction with petroleum ether, ethanol, methanol and water. All the extracts were administered as suspension in 2% gum acacia inall the experiments. In pentylene tetrazole maximal electro shock, strychnine- and picrotoxin-induced convulsion models, the medium and high doses (600 and 800mg/kg) of the extract showed significant anticonvulsant activity [14].

Calotropis procera

The anticonvulsant activity of different root extracts of *Calotropis procera* was studied in rats using seizures induced by maximal electroshock seizures (MES), pentylenetetrazol (PTZ), lithium-pilocarpine and electrical kindling seizures. In the MES test, the chloroform extract of *Calotropis procera* roots showed the most significant ($P<0.01$) anticonvulsant effect, it decreased the duration of hind limb extension (extensor phase), clonus and also the duration of the stupor phase compared with the controls. In the PTZ test, the chloroform extract exhibited a highly significant ($P<0.001$) effect, and the aqueous extract had a significant ($P<0.01$) effect compared with the controls by delaying the onset of convulsions. The extracts also inhibited convulsions induced by lithium-pilocarpine and electrical kindling [15].

Carthamus tinctorius

Subcutaneous administration of 1–10 g/kg bw of an aqueous or 50% methanol extract of the flowers had central nervous system depressant effects and relaxed skeletal muscles in mice. Subcutaneous administration of 10 g/kg bw of a 50% methanol extract of the flowers inhibited pentylenetetrazole-induced convulsions in mice [16].

Cicer arietinum

Different doses of dichloromethane extract of *Cicer arietinum* were administered to the mice, the pentylenetetrazole induced clonic seizure (occurrence and latency) was recorded 30 min thereafter. The extract protected mice against clonic seizures induced by pentylenetetrazole, dose-dependently (ED_{50}= 3g/kg) with no toxic and lethal effects [17-18].

Citrus limon

The central nervous system (CNS) depressant and anticonvulsant activities of *Citrus limon* essential oil (EO) were investigated in animal models. The EO (50, 100 and 150 mg/kg) administered by oral route in mice caused a significant decrease in the motor activity of animals when compared with the control group, up to thirty days after the administration and the dose of 150 mg/kg significantly reduced the remaining time of the animals on the Rota-rod apparatus. Additionally, *C. limon* essential oil was also capable to promote an increase of latency for development of convulsions induced by pentylenetetrazole. The administration of flumazenil, (10 mg/kg, ip), $GABA_A$-benzodiazepine (GABA-BZD) receptor antagonist, antagonized the effect of *C. limon* essential oil at higher dose. *C. limon* essential oil was also capable to promote an increase of latency for development of convulsions induced by picrotoxin at higher dose. In the same way, the anticonvulsant effect of the EO was affected by pretreatment with flumazenil, a selective antagonist of benzodiazepine site of $GABA_A$ receptor [19].

Clitoria ternatea

The spectrum of activity of the methanolic extract of *Clitoria ternatea* (CT) on the CNS was determined. The CT was studied for its effect on cognitive behavior, anxiety, depression, stress and convulsions induced by pentylenetetrazol (PTZ) and maximum electroshock (MES). To explain these effects, the effect of CT was also studied on behavior mediated by dopamine (DA), noradrenaline, serotonin and acetylcholine. The extract decreased time required to occupy the central platform (transfer latency, TL) in the elevated plus maze (EPM) and increased discrimination index in the object recognition test, indicating nootropic activity. The extract was more active in the object recognition test than in the EPM. The extract increased occupancy in the open arm of EPM by 160% and in the lit box of the light/dark exploration test by 157%, indicating its anxiolytic

activity. It decreased the duration of immobility in tail suspension test (suggesting its antidepressant activity), reduced stress-induced ulcers and reduced the convulsing action of PTZ and MES. The extract exhibited tendency to reduce the intensity of behavior mediated via serotonin and acetylcholine. The effect on DA- and noradrenaline-mediated behavior was not significant. Accordingly, the extract possessed nootropic, anxiolytic, antidepressant, anticonvulsant and antistress activity [20].

Coriandrum sativum

The effects of hydroalcoholic extract of aerial parts of the plants (100, 500 and 1000 mg/kg) on brain tissues oxidative damages following seizures induced by pentylenetetrazole (PTZ) was investigated in rats. The extract significantly increased the MCS (latencies to the first minimal clonic seizures) and GTCS (latencies to the first generalized tonic-clonic seizures) ($P<0.01$, $P<0.001$) following PTZ-induced seizures. The malondialdehyde (MDA) levels in both cortical and hippocampal tissues of PTZ group were significantly higher than those of the control animals ($P<0.001$). Pretreatment with the extract prevented elevation of the MDA levels ($P<0.010$ - $P<0.001$). Following PTZ administration, a significant reduction in total thiol groups was observed in both cortical and hippocampal tissues ($P<0.050$). Pre-treatment with the 500 mg/kg of the extract caused a significant decreased in total thiol concentration in the cortical tissues ($P<0.010$). Accordingly, the hydroalcoholic extract of the aerial parts of *Coriandrum sativum* possessed significant antioxidant and anticonvulsant activities [21].

Intraperitoneal injection of decoction and maceration extracts increased the latency of the convulsions induced by PTZ in albino mice, but failed to produce complete protection against mortality. The anticonvulsant activities of high dose extracts were similar to that of phenobarbital at a dose of 20 mg/kg in the PTZ test. In the maximal electroshock seizures, the aqueous extracts of seeds (at a dose of 0.5 g/kg) and the ethanolic extract (at doses of 3.5 and 5 g/kg) decreased the duration of tonic seizures by 22.30%, 30.43% and 36.96%, respectively [22].

The anticonvulsant activities of *Crocus sativus* stigma constituents, safranal and *crocin*, were studied using pentylenetetrazole (PTZ)-induced convulsions in mice. Safranal (0.15 and 0.35 mg/kg body weight, ip) reduced the seizure duration, delayed the onset of tonic convulsions, and protected mice from death. Crocin (22 mg/kg, ip) did not show anticonvulsant activity [23].

Safranal is an effective anticonvulsant, it was an agonist at $GABA_A$ receptors, and the nose to brain delivery via nanoparticle formulation improved its brain delivery [24].

Cuminum cyminum

The effect of the fruit essential oil of Cuminum cyminum on the epileptiform activity induced by pentylenetetrazol (PTZ) was evaluated using intracellular technique. The results demonstrated that extracellular application of the essential oil of Cuminum cyminum (1% and 3%) dramatically decreased the frequency of spontaneous activity induced by PTZ in a time and concentration dependent manner. In addition it showed protection against pentylenetetrazol-induced epileptic activity by increasing the duration, decreasing the amplitude of after hyperpolarization potential (AHP) following the action potential, the peak of action potential, and inhibition of the firing rate [25].

Cuscuta planiflora

The anticonvulsant effect of 80% methanol extract of the plants was investigated in pentylentetrazole induced seizure in mice. Different doses of extracts delayed the onset of seizure ($p<0.01$), but the duration of seizure did not change significantly. Pretreatment of animals with different doses of extracts decreased the mortality rate significantly ($p<0.01$), the percent of seizure protection was also greater than control group significantly ($p<0.05$) The most effective dose was 50 mg/kg[26].

Cynodon dactylon

The ethanol extract of aerial parts of *Cynodon dactylon* showed marked protection against convulsions induced by chemo convulsive agents in mice. The catecholamines contains were significantly increased in the brains of extract treated mice. The amount of GABA, which was most likely to be involved in seizure activity, was increased significantly in mice brain after six week treatment. Results revealed that the extract showed a significant anticonvulsive property by altering the level of catecholamine and brain amino acids in mice [27-28].

The ethanol extract of aerial parts of *Cynodon dactylon* inhibited the onset and the incidence of convulsion in a dose dependent manner against pentylenetetrazole-induced convulsion [29].

Anticonvulsant activity of ethanolic extract of *Cynodon dactylon* was studied against maximal electroshock and Pentylenetetrazol (PTZ) induced convulsions in mice. The extract (200, 400, 600 mg/kg) suppressed hind limb tonic extensions induced by MES and also exhibited protective effect in PTZ-induced seizures[30].

Cyperus rotuntdus

The anticonvulsant activity of *Cyperus rotundus* essential oils was evaluated using MES produced convulsion in rats. The essential oil of *Cyperus rotundus* 500mg/kg, significantly decreased the duration ($p<0.01$), of clonus (12.00 ± 0.7303 s) and stupor (74.20 ± 0.6325 s) phase of MES induced convulsion as compared to control [31].

The anticonvulsant effect of *Cyperus rotundus* extract was also experimentally examined in mice. Mice received *Cyperus rotundus* rhizome extract at three doses (100, 200 and 400 mg/kg; ip). All groups except for control group, were kindled by 11 injections of PTZ (35 mg/kg; ip) with an interval of 48 h. In the 12th injection, all groups except for control group, were tested for PTZ challenge dose (75 mg/kg). The exhibited phases of seizure (0-6) were observed and noted for 30 min after PTZ injection. All brains of mice were removed and then malondialdehyde (MDA), superoxide dismutase (SOD) and nitric oxide (NO) levels of brain tissues were determined. Data analysis showed that the hydroalcoholic extract of *Cyperus rotundus* reduced intensity and duration of seizure and increased the level of SOD and NO and decrease MDA level in mice brain [32].

The anticonvulsant effect of *Cyperus rotundus* roots and rhizomes was studied in seizures induced by pentylenetetrazol (PTZ) and picrotoxin (PTX) in mice. Pretreatment with hydroalcoholic extract of *Cyperus rotundus* roots and rhizomes (50-200mg/kg) induced a dose-dependent decrease in the incidence of both clonic and generalized tonic-clonic seizures ($p\leq0.05$) following PTZ and PTX administration. Co-administration of a sub-effective dose of CR (50 mg/kg, po) with a sub-protective dose of diazepam (0.5 mg/kg, ip) increased the latency to seizure. The combination significantly enhanced percent protection against PTZ and

PTX induced convulsions. The authors suggested that the anticonvulsant effect of *Cyperus rotundus* roots and rhizomes against PTZ and PTX induced convulsions may be mediated, at least partly, through $GABA_A$-benzodiazepine receptor complex [33].

Pretreatment with the ethanol extract of *Cyperus rotundus* caused significant protection against strychnine and leptazol-induced convulsions [34].

Equisetum arvense

In studying of sedative and anticonvulsant effects of Equisetum arvense, hydroalcoholic extract of Equisetum arvense (200 and 400 mg/kg) showed significant activity on the open-field, enhanced the number of falls in the rota-rod reducing the time of permanence in the bar and increased the sleeping time (46% and 74% respectively) in the barbiturate-induced sleeping time. In the pentylenetetrazole-seizure, it increased the first convulsion latency, diminished the severity of convulsions, reduced the percentage of animals which developed convulsion (50% and 25% respectively) and protected animals from death. However, in the elevated plus maze, the doses 50, 100 and 150 mg/kg did not affect the evaluated parameters[35].

Eschscholzia californica

The sedative effects of alkaloids detected in *E.californica* were attributed to chloride-current modulation, which were widely expressed in the brain mainly at the inhibitory interneurons. Electrophysiological studies on a recombinant α_1 β_2 γ_2 $GABA_A$ receptor showed no effect of *N*-methyllaurotetanine at concentrations lower than 30 μM. However, (*S*)-reticuline behaved as positive allosteric modulator at the α_3, α_5, and α_6 isoforms of $GABA_A$ receptors. The depressant properties of aerial parts of *E. californica* were assigned to chloride-current modulation by (*S*)-reticuline at the $\alpha\beta_2\gamma_2$ and $\alpha_5\beta_2\gamma_2$ $GABA_A$ receptors[36].

Protopine, cryptopine and allocryptopine were demonstrated to enhance 3H-gamma-aminobutyric acid (3H-GABA) binding to rat brain synaptic membrane receptors. This effect might be indicate a benzodiazepine-like activity of these alkaloids[37].

***Gossypium* species**

The antiepileptic activity of aqueous extract of *Gossypium herbaceum* (AEGH) at 10, 30, and 100 mg/Kg, po was evaluated by the convulsions induced in mice by maximum electroshock (MES), pentylenetetrazole (PTZ) and isoniazid (INH). In MES method, aqueous extract of *Gossypium herbaceum* inhibited convulsions significantly potent than Diazepam. In PTZ method, aqueous extract of *Gossypium herbaceum* inhibited convulsions potent than phenobarbitone sodium. In INH method, aqueous extract of *Gossypium herbaceum* delayed the onset of convulsions with a potency less than Diazepam[38].

Hibiscus rosa-sinensis

The ethanolic extracts of flowers of *Hibiscus rosa sinesis* exhibited anticonvulsant activity. The bioassay guided fractionation indicated that the anticonvulsant activity lies in the acetone soluble part of ethanolic extract of H. rosa sinesis flowers. The fraction protected animals from maximum electro shock,

electrical kindling and pentylenetetrazole-induced convulsions in mice and inhibited convulsions induced by lithium-pilocarpine and electrical kindling. It antagonised the behavioral effects of D-amphetamine and potentiated the pentobarbitone-induced sleep. It raised brain contents of gamma-aminobutyric acid (GABA) and serotonin[39].

Hyoscyamus niger

The anticonvulsant effects of alcoholic extract of *Hyoscyamus niger* seed in doses of 50, 100 and 200 mg/kg ip, was evaluated in seizure induced by Pentylene tetrazole. The results showed that administration of Hyoscyamus niger seed extract possessed inhibitory effect on the steps, progression and duration of seizure, especially in the last steps of convulsion. However, therapy with henbane seed extract resulted in an efficient anticonvulsive effect from the 8^{th} injection reaching the highest level of efficiency at the 12^{th} ($p<0.001$)[40].

The effects of methanolic extract of *Hyoscyamus niger* on seizures induced by picrotoxin was studied in mice. Groups of mice were pretreated with methanolic extract of the plant (12.5, 25, 50, 100, 200, 300, 400 mg/kg, ip), 20 minutes prior to the picrotoxin (12 mg/kg, ip)-induced seizures. The latency of seizure (sec), duration of seizure (sec) and mortality rate were determined in test and control groups. The results showed that latency of seizure was increased in groups pretreated with 100, 200, 300 and 400 mg/kg of extract, furthermore, methanolic extract also (200-400 mg/kg) significantly ($P<0.01$) delayed the death time in mice as compared to control[41].

Juglans regia

The potential anticonvulsant effect of walnut kernel extract (WKE) was evaluated in pentylenetetrazole (PTZ; 2 mg/ml/min) induced seizures in rats. WKE administration significantly increased the PTZ dose needed to induce the first myoclonic jerk (13.09 ± 1.29 vs. 49.71 ± 12.03 mg/kg; $p < 0.001$), decreased the severity of seizure grades and reduced the mortality rate to 0%. Flumazenil (FMZ; 5 mg/kg ip), did not significantly reduce the anticonvulsant effect of WKE. The combination of diazepam (DPZ; 0.5 mg/kg ip) and WKE showed a synergic anticonvulsant effect, whereas ethosuximide (ESM) had no significant influence ($p > 0.05$) on the WKE effects. It seemed that the anticonvulsant effect attributed to signaling pathways other than benzodiazepine mediated γ-aminobutyric acid receptors[42].

Juniperus oxycedrus

Pretreatment with methanol and dicliloromethanol extracts (200 mg/kg) did not modify the duration of convulsions induced by electrical stimulation in mice[43].

Plants with antidepressant activity:

Apium graveolens

The anti-depressant effect of methanolic extract of *Apium graveolens* seeds (AGM) was investigated using two behavioral models in *in-vivo* study, the AGM (100, 200 mg/kg) produced significant anti-depressant effect on mice and rats in both forced swim test and tail suspension test , its action was found to be similar to imipramine. The anti-depressant effects of AGM were more prominent at 200 mg/kg when compared to lower dose of same fraction. The 3, n-butylphthalide and sedanenolide isolated from celery oil showed weak sedative activity, prolonged pentobarbital narcosis, and induced sleep immediately following recovery from a prior barbiturate treatment in mice [44].

Avena sativa

The dried seeds and fresh plant exerted antidepressant activity, and it was useful where lowered mood is associated with anxiety and nervous exhaustion, especially during menopause. The fresh plant is a tonic remedy for all types of nervous debility, and can help to improve sleep duration and quality where the person is literally too tired to sleep. Oats also aid withdrawal from tobacco and drug addiction [45]. A dose of 1600 mg of oat herb extract acutely improve attention and concentration and the ability to maintain task focus in older adults with differing levels of cognitive status [46].

Bacopa monniera

Bacosides A and B, bacopasides I and II and bacopasaponin C and the extract of *Bacopa monniera* exhibited antidepressant activity, while bacopaside VII did not have any antidepressant activity when tested on forced swimming and tail-suspension models in experimental animals[47-49].

Benincasa hispida

The antidepressant activity of the methanolic extract (50, 100, and 200 mg/kg, administered orally for 14 successive days) was tested in Swiss male albino mice incomparison with classical antidepressant drugs

(imipramine 15 mg/kg, fluoxetine 20 mg/kg, and phenelzine 20 mg/kg). The methanolic extract of *B. hispida* showed significant antidepressant-like activity in mice probably by inhibiting MAO-A, and through interaction with dopaminergic, α1- adrenergic, serotoninergic, and GABAergic systems [50].

Citrus limon

Anxiolytic and antidepressant effects and acute toxicity of ethanolic extract (EE) of the aerial parts of *Citrus limon* were studied in mice. Anxiolytic activity was evaluated using open field and elevated plus-maze tests. The antidepressant effect of the extract was studied by forced swimming test in mice. In the open field test, the oral route administration of EE alone showed significant sedative and antidepressant activities in mice ($p < 0.05$). EE did not alter motor coordination. The EE, at three doses tested, showed antidepressant effect and produced decrease in immobility time. The authors concluded that the EE of the aerial parts of *C. limon* have a sedative effect, which may be mediated by benzodiazepine-type receptors, and also an antidepressant effect where noradrenergic and serotoninergic mechanisms will probably play a role [51].

The sedative, anxiolytic and antidepressant effects of essential oil (EO) of leaves from Citrus limon were investigated in mice. The effects of EO were demonstrated by open-field, elevated-plus-maze, rota rod, pentobarbital-induced sleeping time, and forced swimming tests in mice. In the open-field test, EO at the doses of 50, 100 and 150 mg/kg, after oral administration, significantly decreased the number of crossings, grooming, and rearing. In the elevated-plus-maze (EPM) test, EO increased the time of permanence and the number of entrances in the open arms. On the contrary, the time of permanence and the number of entrances in the closed arms were decreased. In the rota rod test, EO did not alter motor coordination and, thus, was devoid of effects, as related to controls. In the pentobarbital-induced sleeping time test, EO at the same doses significantly increased the animals sleeping time duration. Since EO, at the doses of 50, 100 and 150 mg/kg, did not show a sedative effect in the open field test, these three doses when used in the forced swimming test, they were producing a decrease in the immobility time, similarly to that of imipramine (positive control). However, the antidepressant effects of EO were not altered by the previous administration of paroxetine. In addition, effects of EO in the forced swimming test were totally blocked by reserpine pretreatment [52].

The behavioral effects of *Citrus limon* juice was studied in rats at three different doses (0.2, 0.4 and 0.6 ml/kg), considered as low, moderate and high doses. Anxiolytic and antidepressant activities were specifically assessed twice during 15 days using open field test, elevated plus maze and forced swimming test. In open field test Citrus limon, revealed increase in distance travelled, number of central entries and number of rearing's at moderate dose, while in the elevated plus maze, number of open arm entries were found to be increased. Whereas in forced swimming test, there was decrease in duration of immobility and increase in duration of climbing [53].

Clitoria ternatea

The effectiveness of *Clitoria ternatea* in the treatment of obsessive-compulsive was carried out experimentally. The influence of ethanolic extract of *Clitorea ternatea* was evaluated in marble-burying behavior in mice. The results revealed that ethanolic extract of *Clitorea ternatea* (EECT) (100, 200 and 400mg/kg) reduced the marble burying behavior in mice. It was clear that EECT exhibited significant anti-compulsive effect in marble-burying behavior test in mice and the effect may be attributed to enhanced serotonergic function and might have influence on 5-HT reuptake [54].

A Perment polyherbal Ayurvedic formulation that contains equal parts of *Clitoria ternatea*, *Withania somnifera* Dun., *Asparagus racemosus* Linn., *Bacopa monniera* Linn., is used clinically as mood elevators. The behavioural effects and the possible mode of action of Perment was studied in stress induced depressive model. Chronic unpredictable mild stress (CUMS) was used to induce depression in rats. Open field exploratory behaviour, elevated plus maze, social interaction and behavioural despair tests were used to assess behaviour. Plasma noradrenaline, serotonin, corticosterone and brain/adrenal corticosterone levels were measured to support the behavioural effects of Perment. Exposure to CUMS for 21 days caused anxiety and depression in rats, as indicated by significant decrease in locomotor activity in the open field exploratory behaviour test and increased immobility period in the behavioural despair test. Perment predominantly exhibited antidepressant action than anxiolytic activity. Furthermore, Perment increased the plasma noradrenaline and serotonin levels in stressed rats. No significant alteration in the brain corticosterone level in stressed rats was observed with Perment treatment. However the adrenal corticosterone level was decreased with Perment. It can be concluded that the Perment formulation exhibited synergistic activity, has a significant antidepressant and anxiolytic activity, which may be mediated through adrenergic and serotonergic system activation [55].

Coriandrum sativum

Diethyl ether extract of seeds of *Coriandrum sativum* showed more significant antidepressant effect than that of aqueous extract through interaction with adrenergic, dopamine-ergic and GABA-ergic system [56].

Crocus sativus

The antidepressant properties of stigmas and corms of *Crocus sativus* was studied experimentally. The aqueous ethanol extract of *Crocus sativus* corms was fractionated on the basis of polarity. Among the different fractions, the petroleum ether and dichloromethane fractions at doses of 150, 300, and 600 mg/kg showed significant antidepressant-like activities in dose-dependent manners, by means of behavioral models of depression. The immobility time in the forced swimming test and tail suspending test was significantly reduced by the two fractions, without accompanying changes in ambulation when assessed in the open-field test. By means of a gas chromatography-mass spectrometry technique, twelve compounds of the petroleum ether fraction were identified. Aqueous stigmas extract also exerted antidepressive effects in the behavioral models. Crocin 1 and crocin 2 of the aqueous stigmas extract were identified by a reversed-phase HPLC analysis. The data indicated that antidepressant-like properties of aqueous stigma extracts attributed to crocin 1 [57-58].

The efficacy of hydroalcoholic extract of *Crocus sativus* (stigma) in comparison with fluoxetine in the treatment of mild to moderate depression was studied in a 6-week double-blind, randomized trial. Forty adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition for major depression based on the structured clinical interview for DSM-IV and with mild to moderate depression were participated in the trial. Patients were randomly assigned to receive capsules of saffron 30 mg/day (BD) (Group 1) and capsule of fluoxetine 20 mg/day (BD) (Group 2) for a 6-week study. Saffron at this dose was found to be effective similar to fluoxetine in the treatment of mild to moderate depression ($F = 0.13$, d.f. = 1, $P = 0.71$). There were no significant differences between the two groups in terms of observed side effects [59].

The efficacy of petal of *Crocus sativus* was compared with fluoxetine in the treatment of depressed outpatients in an 8-week pilot double-blind randomized trial. Forty adult outpatients who met the DSM- IV criteria for major depression based on the structured clinical interview for DSM- IV were participated in the trial. Patients have a baseline Hamilton Rating Scale for Depression score of at least 18. In this double-blind and randomized trial, patients were randomly assigned to receive either capsule of petal of *Crocus sativus* 15 mg bid (morning and evening) or fluoxetine 10 mg bid (morning and evening) for a 8-week. At the end of trial, petal of *Crocus sativus* was found to be effective similar to fluoxetine in the treatment of mild to moderate depression ($F=0.03$, d.f.=1, $P=0.84$). In addition, in the both treatments, the remission rate was 25%. There were no significant differences in the two groups in terms of observed side effects [60].

The non selective serotonin (5-HT) receptor agonist mCPP is known to induce obsessive–compulsive disorder (OCD-like) behavior (excessive self-grooming) in rodents and exacerbated symptoms in patients with OCD. Crocins (30 and 50 mg/kg, ip) in rats attenuated mCPP-induced excessive self-grooming. The results also indicated that the effects of crocins on an animal model of OCD cannot be attributed to changes in locomotor activity, the effect could be attributed to interaction between crocins and the serotonergic system [61].

In a randomized, double-blind study, 30 mg of saffron extract (in capsules) given for 6 weeks resulted in significant alleviation of depression compared to placeb group, and no side effects were recorded. Many follow-up double blind trials carried out on saffron preparation compared with imipramine and fluoxetine; showed that saffron possessed antidepressant effects [59, 62-64].

The molecular mechanism of antidepressant effect of aqueous extract of saffron and its effect on the levels of brain-derived neurotrophic factor (BDNF), VGF neuropeptide, cyclic-AMP response element binding protein (CREB) and phospho-CREB (p-CREB) in rat hippocampus, were investigated. The aqueous extract of saffron (40, 80 and 160 mg/kg/day) and imipramine 10 mg/kg/day were injected intraperitoneally (ip) for 21 days to rats. The FST (forced swimming test) was performed on the days 1^{st} and 21^{st}. The results of FST showed that saffron reduced the immobility time. The protein levels of BDNF, CREB and p-CREB were significantly increased in saffron treated rats. VGF protein expression was also increased, but not significantly. The transcript levels of BDNF was also significantly increased. No significant changes in CREB and VGF transcript levels were observed. The authors concluded that aqueous extract of saffron has antidepressant effects and the mechanism of its antidepressant effect may be due to increasing the levels of BDNF, VGF, CREB and P-CREB in rat hippocampus [65].

Cuscuta planiflora

The effects of *Cuscuta planiflora* (500mg capsules) were evaluated in patients with major depression by a randomized triple-blind controlled clinical trial. Patients were taken the treatment for 8 weeks. Depression was measured before and after the study by Beck depression inventory and Hamilton depression inventory. There was a significant decrease in mean scores of Beck and Hamilton depression inventories in the group treated by Cuscuta planiflora ($p<0.01$) compared with control[66].

Daucus carota

The antidepressant potential of ethanol root extract of *Dacus carota* (DC) was studied in different animal models, forced swim test (FST), tail suspension test (TST), apomorphine induced hypothermia (AIH), reserpine induced hypothermia (RIH), 5-HTP potentiation of head twitches (HTPPH) in mice. Fluoxetine (25 mg/kg) was used as a standard drug in FST, TST and HTPPH models and desipramine (20 mg/kg) was used as a standard drug in AIH and RIH models. The antidepressant activity of DC (400 mg/kg) was comparable to that of standard drugs[67].

Eschscholtzia californica

The aqueous-alcoholic extract from *Eschscholtzia californica* inhibited the enzymatic degradation of catecholamines as well as the synthesis of adrenaline. The extract also dramatically shorten the lag phase in the catalysis of phenolase probably due to their o-diphenol content, furtheremore, dopamine beta-hydroxylase, monoamine oxidase (MAO-B) and diamine oxidases were inhibited by Eschscholtzia californica extracts. These mechanisms could explain the antidepressive and hypnotic activities of Eschscholtzia californic[68].

The protopine was also act as an inhibitor of both serotonin transporter and noradrenaline transporter in vitro assays. 5-hydroxy-DL-tryptophan(5-HTP)-induced head twitch response (HTR) and tail suspension test were adopted to study whether protopine has anti-depression effect in mice using reference antidepressant fluoxetine and desipramine as positive controls. In HTR test, protopine at doses of 5, 10, 20 mg/kg dose dependently increase the number of 5-HTP-induced HTR. Protopine at doses of 3.75 mg/kg, 7.5 mg/kg and 30 mg/kg also produces a dose-dependent reduction in immobility in the tail suspension test[69].

Foeniculum vulgare

The antidepressant effect of *Vetiveria zizanioides* and *Foeniculum vulgare* in comparison with antidepressant drug fluoxetine was investigated in depressive behavior in albino rats. Both Forced swimming test and Tail suspension test were used for screening antidepressant effect. The ethanolic extract of *Vetiveria zizanioides*(100mg/kg) and *Foeniculum vulgare* (200mg/kg) together, fluoxetine(10mg/kg) and saline were administered 30mts prior to the tests and the immobility period was recorded for 6mts.The antidepressant effect of both were compared to that of fluoxetine. *Vetiveria zizanioides*(100mg/kg) and *Foeniculum vulgare* (200mg/kg) produced significant antidepressant effect by reduction in immobility period as compared to control. But as a group together they are equally effective as fluoxetine (10mg/kg)[70].

The antidepressant effects of methanolic extract of *Foeniculum vulgare* fruits (MEFV) was investigated using force swim test in rats (FST), potentiation of norepinephrine (NE) toxicity in mice and haloperidol induce catalepsy (HIC) in mice. The extract of *F.vulgare* (250 and 500 mg/kg) was administered orally to rats used in FST and 500mg/kg was administered in HIC and same dose administered in NE toxicity in mice. The dose of 250mg/kg and 500mg/kg of extract significantly ($p<0.001$) reduced the immobility times in rats, 500 mg/kg showed more potent effect than imipramine (30mg/kg). In NE toxicity model it was observed that MEFV dose not interfere with adrenergic system. A significant ($P<0.001$) reduction in the duration of catalepsy was observed in the MEFV treated group and Fluoxetine group as compared to the haloperidol treated group. In HIC, mice were sacrificed on the seventh day and TBARS, glutathione, nitrite activities were estimated. Monoamine oxidase inhibiting effect and anti-oxidant effect of *Foeniculum vulgare* may be contributing favorably to the antidepressant-like activity[71].

Glycyrrhiza glabra

The effects of aqueous extract of *Glycyrrhiza glabra* on depression was investigated in mice using forced swim test (FST) and tail suspension test (TST). The extract of *G. glabra* (75, 150, and 300 mg/kg) was administered orally for 7 successive days in separate groups of male mice. The dose of 150 mg/kg of the extract significantly reduced the immobility times of mice in both FST and TST, without any significant effect on locomotor activity of mice. The efficacy of extract was found to be comparable to that of imipramine (15 mg/kg ip) and fluoxetine (20 mg/kg ip). Liquorice extract reversed reserpine-induced extension of immobility period of mice in FST and TST. Sulpiride (50 mg/kg ip, a selective D_2 receptor antagonist) and prazosin (62.5 µg/kg ip, an α_1-adrenoceptor antagonist) significantly attenuated the extract-induced antidepressant-like effect in TST. On the other hand, *p*-chlorophenylalanine (100 mg/kg ip, an inhibitor of serotonin synthesis) did not reverse antidepressant-like effect of liquorice extract. It seemed that the antidepressant-like effect of liquorice extract mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin[72].

***Gossypium* species**

Aqueous extract of detoxified *Gossypium herbaceum* seeds showed antidepressant-like effect due to activation of adenyl cyclase-cAMP pathway in signal transduction system. Aqueous extract of detoxified *Gossypium herbaceum* seeds 0.01, 0.03, 0.10, 0.30 mg/ml was incubated directly with the synaptic membrane

extracted from the cerebral cortex in rats, and adenylyl cyclase activity was detected by radio-immunoassay. Antidepressant and anxiolytic effects of the aqueous extract of detoxified *Gossypium herbaceum* seeds were caused by activation of AC-cAMP pathway in signal transduction system, thus protecting neurons from the lesion[73-74].

***Haplophyllum* species**

The oil showed weakly acetylcholinesterase (AChE) inhibitory activity, compared to standard substances, whereas no inhibition on butyrylcholinesterase (BuChE) activity was observed[75]. The inhibitory activity of acetyl cholinestrase was mainly accumulated in the chloforom and ethyl acetate fractions of different parts extracts of H. tuberculatum. The most active was the stem ethyl acetate fraction with an inhibitory effect of 79% and IC_{50} of 0.45 µg/ml. Other fractions possessed an inhibitory effect at arrange between 70 – 77%[76].

Helianthus annuus

The methanolic extract of *Helianthus annuus* seeds also caused remarkable antidepressant activity (tail suspension test). *H. annuus* showed significant antidepressant activity ($p<0.05$) by decreasing the immobility time (*H. annuus* 100mg/kg, 93±0.47; *H. annuus* 200mg/kg, 78±1.3) as compared with Imipamine (60mg/kg, 30.2±0.64) and control (190.8±0.75)[77].

Hibiscus rosa-sinensis

The anti-depressant activity of methanol extract containing anthocyanins (MHR) (30 and 100 mg/kg) and anthocyanidins (AHR) (30 and 100 mg/ kg) of H. rosa-sinensis flowers were evaluated in mice using behavioral tests [tail suspension test (TST) and forced swim test (FST)]. The mechanism of action involved in antidepressant activity was investigated by observing the effect of extract after pre-treatment with low dose haloperidol, prazosin and para-chlorophenylalanine (p-CPA). The results revealed that extract caused significant decrease in immobility time in TST and FST, similar to that of imipramine (10 mg/kg, ip) which served as a positive control. The extract significantly attenuated the duration of immobility induced by Haloperidol (50 µg/ kg, ip., a classical D(2)-like dopamine receptor antagonist), Prazosin (62.5 µg/kg, ip, an α1-adrenoceptor antagonist) and p-chlorophenylalanine (100 mg/kg, ip, × 3 days; an inhibitor of serotonin synthesis) in both TST and FST[78].

Hyoscyamus niger

The antidepressant effect of *Hyoscyamus niger* was evaluated in animal models [forced swim test (FST) and tail suspension test (TST) in mice] of depression with studying the possible mechanism underlying the antidepressant effect. Locomotor and anxiolytic activity was also studied. *Hyoscyamus niger* leaves ethanolic extract was administered to mice by oral route at dose of 25, 50, 100, 200 and 400 mg/kg for 14 days. Further an interaction of *Hyoscyamus niger* ethanolic extract with conventional antidepressant drugs were also studied at sub-effective doses. The ethanolic extract significantly reduced immobility duration of mice in FST and TST. The same doses did not change the motor activity in mice. However, high dose of extract showned anxiolytic activity. Interaction study with conventional antidepressant drugs reduced the duration of immobility count suggested, possible involvement of biogenic amine in antidepressant action[79].

Juglans regia

The antidepressant effect of *Juglans regia* fruit extract (100 and 150 mg/kg bw) was studied in animal models of depression (forced swimming test and tail suspension test). Both doses significantly decreased duration of immobility in both models of depression. The effect of extract was less significant than standard drug fluoxetine. The antidepressant activity could be attributed to the presence of omega 3 fatty acid in extract[80].

III. Plant with sedative and anxiolytic effects:

Anthemis nobelis

In mice, apigenin had a clear affinity for central benzodiazepine receptors. Apigenin competitively inhibited the binding of flunitrazepam, a benzodiazepine, but had no effect on muscarinic receptors, alpha 1-adrenoceptors, or the binding of muscimol to GABA receptors. Apigenin had clear anxiolytic activity in mice without incidence of sedation or muscle relaxation effects at doses similar to those used for classical benzodiazepines; no anticonvulsant action was detected. Increasing dosages produced mild sedation and a reduction in ambulatory locomotor activity [81-82].

Arachis hypogaea

Arachis hypogaea leaf aqueous extracts have received a long reputation as an abirritative remedy to ease various sleep disorders. The clinical studies confirmed the hypnotic effects of *Arachis hypogaea* [83-84].The sedative effects of *Arachis hypogaea* leaf aqueous extracts on brain ATP, AMP, adenosine and glutamate/GABA of rats was investigated. Intragastrically administrated *Arachis hypogaea* leaf aqueous extracts(PLAE , 100 and 500 mg/kg body weight BW) and peanut stem aqueous extracts (PSAE, 500 mg/kg BW) for at least 14 days showed that brain lactate were significantly elevated ($p < 0.05$) in rat cerebrums after PLAE administrations, compared with control and PSAE groups. A significant degradation of the brain adenosine triphosphate (ATP) ($p < 0.05$) was observed in the brain-stems and even the whole brains of rats of PLAE treatments. Moreover, the brain adenosine monophosphate (AMP) were clearly decreased ($p < 0.05$) in rat cerebrum and brainstem regions, while the brain adenosine revealed an increasing propensity ($p = 0.076$) in the cerebrums of freely behaving rats. The γ-aminobutyric acid (GABA) concentrations were statistically ($p < 0.05$) enhanced and the ratios of Glutamate/GABA were simultaneously reduced ($p < 0.05$) in rat brainstems, no matter which dose (100 or 500 mg/kg BW) of PLAE were used [85].

Arctium lappa

The anti-fatigue effect of the extract of *Arctium lappa* L. was studied in male mice by forced swimming test. The swimming time of mice treated by 4 and 6 g/kg of an extract of *Arctium lappa* was significantly prolonged as compared with control group. The hepatic glycogen storage in the groups treated with 2, 4 and 6 g/kg of *Arctium lappa* extract was significantly increased. Lactic acid clearance in the groups treated with 4, and 6 g/kg of *Arctium lappa* extract was significantl**y** accelerated after mice swimming [86].

Asparagus officinalis

Asparagus officinalis exerted antifatigue effects, enhanced anoxia tolerance, induced analgesia and improved memory, as well as decreased the contents of lipid peroxide in plasma, liver and brain of the animal [87].

Avena sativa

An extract of wild green oat (*Avenasativa* L.), was tested *in vivo* in rats for its behavioural effects after chronic oral administration via extract-admixed food. Rats received 10 g/kg and 100 g/kg extract-admixed food showed slight decreased food and fluid intake in the high dose group , with no side effects observed during the treatment. The low dose led to an improvement of active stress response, an enhancement of shock avoidance learning and an increased synchrony in social behavior [88].

Dietary oat β-glucan enhanced the endurance capacity of rats and facilitated their recovery from stress and fatigue. Sparsgue-Dawley rats, fed with/without oat β-glucan 312.5 mg/ kg/day for 7 weeks, were subjected to run on a treadmill system to make them exhausted. All rats were immediately sacrificed after prolonged exercise, and the major metabolic substrates were measured in serum and liver. The results showed feeding dietary oat β-glucan to rats significantly reduce the body weight and increase the maximum running time compared with normal control ($P<0.05$). Furthermore, dietary oat β-glucan decreased the levels of blood urea nitrogen, lactate acid, and creatine kinase activity in serum, and increased the levels of non-esterified fatty acids, lactic dehydrogenase activity in serum, and the content of liver glycogen [89].

Avenasativa improved overall mental fitness and supported cognitive performance in stressful situations. *Avenasativa* has been shown to positively affect the activity of brain enzymes closely related to mental health and cognitive function in-vitro. Additionally, preclinical and clinical studies have confirmed that *Avena sativa* specifically interacted with brain structures and neurotransmitters implicated in cognition, memory and motivation. *Avena sativa* boasted a dual activity profile on monoamino oxidase-B(MAO-B*)* and phosphodiestrase 4 (PDE4)thus displayed in its ability to meditate a strengthening and balancing effect on the brain and mind [90].

Bacopa monniera

Crude plant extract of *Bacopa monnieri* or bacosides have also shown anxiolytic effects, antidepressant activity, anticonvulsive action and antioxidant activity[91].

Bacopa monnieri was highly effective as an adaptogen, it normalized acute and chronic stress induced corticosterone changes in rats. It also normalized noradrenalin (NA), 5-HT, and DA in cortex and hippocampus of rats in acute and chronic unpredictable stress[92].

Bacopa monniera lowered norepinephrine and increases the 5-hydroxytryptamine levels in hippocampus, hypothalamus and cerebral cortex. The higher doses of *Bacopa monniera* extracts produced significantly greater anxiolytic effects compared to lorazepam, a standard anxiolytic drug from benzodiazepine

group [93]. However, acute and sub chronic (one week) treatment of *Bacopa monnieri* methanolic extract (10, 20 or 30 mg/kg) didn't affected dopamine (DA) and serotonin (5-HT) turnover in mice whole brain[94-95].

Ballota nigra

Phenylpropanoid derivatives isolated from *Ballota nigra* showed neurosedative activity and exhibit potent antioxidant activities which are of therapeutic interest [96]. The ability of five phenylpropanoids (verbascoside, forsythoside B, arenarioside, ballotetroside, and caffeoyl malic acid) isolated from a hydroalcoholic extract, to bind to benzodiazepine, dopaminergic, and morphinic receptors was investigated. To carry out these studies, affinity tests with rat striata, entire brains and receptor rich preparations were employed. Results show that four of the five compounds are able to bind to the studied receptors. Inhibitory concentrations at 50% were determined and vary from 0.4 to 4.7 mg/ml. This may be in relation with the *Ballota nigra* known neurosedative activities [97].

Bryophyllum calycinum

The methanolic extract of *Bryophyllum calycinum* Salisb showed neuro-pharmacological effects in experimental animals (rats and mice). The fraction produced alteration of behavior pattern, caused dose-dependent potentiation of pentobarbitone sleeping time and had significant analgesic activity and possesses a potent CNS depressant action. The saline leaf extract of *Bryophyllum calycinum* Salisb produced a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis, reduction of exploratory activities in the head-dip and evasion tests. Moreover, a dose-dependent muscle in-coordination was observed in the inclined screen, traction and climbing tests in mice. The saline leaf extract produced a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis, reduction of exploratory activities in the head-dip and evasion tests and a dose-dependent muscle incoordination in the inclined screen, traction and climbing tests[98-100].

Caesalpinia crista

The anxiolytic activities of seed extract of Caesalpinia crista in experimental animals, mice and rats were investigated by stair-case model, Three doses (400, 600 and 800mg/kg) showed a significant and dose dependent anxiolytic activity by increasing the number of steps climbed, without any significant effect on rearings by all the three doses. Similarly in EPM model medium, high doses, but not the low dose had significantly enhanced both number of entries and time spent in open arms and decreased in number of entries and time spent in closed arms. In Hole- board model, medium and high doses 600 and 800mg/kg but not the low dose 400mg/kg had significantly enhanced the number, latency and the duration of head dipping but not the rearings. However in LDT model high doses 800mg/kg had significantly exhibited anxiolytic activity by increasing time spent, number of crossings in light compartment and decreased the time spent in dark compartment and decreased the number of rearings in both light and dark compartments. In OFT models, medium and high doses 600 and 800mg/kg but not the low dose 400mg/kg had significantly enhanced total locomotion, central locomotion, number of grooming but the immobility time has drastically reduced. All doses have not exerted any significant effect with rearing, defecation and urination. Moreover in Mirror-chamber model of anxiety, both medium and high doses 600 and 800mg/kg but not the low dose 400mg/kg had significantly reduced the time latency to enter into the mirror chamber and increased the number of entries and time spent in the chamber. These result confirmed the anxiolytic activity of Caesalpinia crista [101].

Caesalpinia crista seed extracts were screened for adaptogenic activity using cold stress and swim endurance models. The seed coat as well as kernel extracts administered orally at a dose of 300mg/kg significantly increased the swim endurance time. The extracts also corrected hyperglycemia, the depletion in serum cortisol level, increased total leukocyte count, and controlling the hyperlipidaemic condition associated with to stress [102].

Carum carvi

The aqueous extract of Carum carvi was evaluated for antistress activity in normal and stress induced rats. The extract was studied for nootropic activity in rats and in vitro antioxidant potential to be correlated with its antistress activity. For the evaluation of antistress activity groups of rats were subjected to forced swim stress one hour after daily treatment of Carum carvi extract. Urinary vanillylmandelic acid (VMA) and ascorbic acid were selected as non invasive biomarkers to assess the antistress activity. The 24 h urinary excretion of vanillylmandelic acid (VMA) and ascorbic acid was determined in all groups under normal and stressed conditions. The nootropic activity of the extract as determined from acquisition, retention and retrieval in rats was studied by conditioned avoidance response using Cook's pole climbing apparatus. Daily administration of Carum carvi at doses of 100, 200 and 300 mg/kg body weight one hour prior to induction of stress inhibited the stress induced urinary biochemical changes in a dose dependent manner. However no change in the urinary

excretion of VMA and ascorbic acid was observed in normal animals. The cognition, as determined by the acquisition, retention and recovery in rats was observed to be dose dependent. The *in vitro* antioxidant activity was determined based on the ability of *Carum carvi* to inhibit lipid peroxidation in liver and brain homogenates. The extract produced significant inhibition of lipid peroxide formation in comparison with ascorbic acid in a dose dependent manner in both liver and brain [103].

Citrus species

The effects of apigenin, a bioflavonoid widely found in citrus fruits, on behavioral changes and inflammatory responses induced by chronic unpredictable mild stress (CUMS) was investigated in rats. When GW9662, a selective peroxisome proliferator-activated receptor gamma (PPARγ) inhibitor, administered 30min before apigenin, apigenin (20mg/kg, intragastrically) for three weeks remarkably ameliorated CUMS-induced behavioral abnormalities, such as decreased locomotor activity and reduced sucrose consumption. In response to oxidative stress, the NLRP3 inflammasome was activated and IL-1β secretion increased in the prefrontal cortex (PFC) of CUMS rats. However, apigenin treatment upregulated PPARγ expression and downregulated the expression of NLRP3, which subsequently downregulated the production of IL-1β. In addition, GW9662 diminished the inhibitory effects of apigenin on the NLRP3 inflammasome. Accordingly, the results demonstrated that apigenin exhibited antidepressant-like effects in CUMS rats, possibly by inhibiting IL-1β production and NLRP3 inflammasome expression via the up-regulation of PPARγ expression [104].

The sedative effects of essential oil (EO) of leaves from Citrus limon were investigated in mice. EO 150 mg/kg, orally significantly increased the animals sleeping time duration [105].

The effects of *Citrus sinensis* essential oil was evaluated in the elevated plus-maze followed by the light/dark paradigm in rats. The animals were exposed to the orange aroma (100, 200 or 400 microl) for 5 min, while in a Plexiglas chamber and were then immediately submitted to the behavioural tests. At all doses, *C sinensis* oil demonstrated anxiolytic activity in at least one of the tests and, at the highest dose, it presented significant effects in both animal models, as indicated by increased exploration of the open arms of the elevated plus-maze (time: $p=0.004$; entries: $p=0.044$) and of the lit chamber of the light/dark paradigm (time: $p=0.030$). In order to discard the possibility that this outcome was due to non-specific effects of any odour exposure, the behavioural response to Melaleuca alternifolia essential oil was also evaluated, using the same animal models, but no anxiolytic effects were observed [106].

Coriandrum sativum

The anxiolytic effect of aqueous extract (50, 100, 200 mg/kg, ip) was examined in male albino mice using elevated plus- maze as an animal model of anxiety. In the elevated plus-maze, aqueous extract at 200 mg/kg showed an anxiolytic effect by increasing the time spent on open arms and the percentage of open arm entries, compared to control group [107-108].

The anxiolytic effect of *Coriandrum sativum* (CS) aqueous extract was evaluated in mice. The antianxiety effect was assessed by elevated plus maze (EPM). In EPM, 50, 100, and 200 mg/kg of CS were significantly ($P<0.001$) increases the number of entries in open arms compared to control. The time spent in open arms also increased in all the doses of CS extract significantly [109].

The anti-anxiety activity of hydroalcoholic extract of *Coriandrum sativum* was studied using different animal models (elevated plus maze, open field test, light and dark test and social interaction test) of anxiety in mice. Diazepam (0.5 mg/kg) was used as astandard drug and hydroalcoholic extract of *Coriandrum sativum* fruit was used in dose of (50, 100 and 200 mg/kg) to study the antianxiety effect. Results revealed that the extract of *Coriandrum sativum* at 100 and 200 mg/kg dose produced anti-anxiety effects almost similar to diazepam, while, at 50 mg/kg dose, it did not produce anti-anxiety activity in all models [110].

The anxiolytic effect of the aqueous extract of *Coriandrum sativum* seed and its effect on spontaneous activity and neuromuscular coordination were evaluated in mice. The anxiolytic effect of aqueous extract (10, 25, 50, 100 mg/kg, ip) was examined in male albino mice using elevated plus-maze as an animal model of anxiety. The effects of the extract on spontaneous activity and neuromuscular coordination were assessed using Animex Activity Meter and rotarod. In the elevated plus-maze, 100 mg/kg of the aqueous extract showed an anxiolytic effect by increasing the time spent on open arms and the percentage of open arm entries, compared to control group. Aqueous extract at 50, 100 and 500 mg/kg significantly reduced spontaneous activity and neuromuscular coordination, compared to control group [111-112].

The aqueous, hydroalcoholic extracts and essential oil of coriander seeds possessed sedative-hypnotic activity. The aqueous, hydroalcoholic extracts and essential oil of coriander seeds (100, 200, 400 and 600 mg/kg) were intraperitoneally administered to male albino mice, 30 minutes before pentobarbital injection (40 mg/kg). Latency to sleep and sleep duration were recorded. Aqueous extract prolonged pentobarbital-induced sleeping time at 200, 400 and 600 mg/kg. Hydroalcoholic extract at doses of 400 and 600 mg/kg increased

pentobarbital induced sleeping time compared to saline-treated group. The essential oil increased pentobarbital-induced sleeping time only at 600 mg/kg [113].

The sleep-prolonging effect of *Coriandrum sativum* was investigated in mice. The hydroalcoholic extract (HAE) and its three fractions, water (WF), ethyl acetate (EAF) and N-butanol (NBF) were prepared from *Coriandrum sativum* aerial parts and administrated to mice. The HAE, EAF and NBF significantly prolonged sleep duration. Only the NBF was significantly decreased sleep latency. No decrease in the neuronal surviving was observed either by HAE or by its fractions. The data indicated that *Coriandrum sativum* exerted sleep-prolonging action without major neurotoxic effect [114].

Crocus sativus

The anxiolytic and hypnotic effects of saffron aqueous extract and its constituents, crocin and safranal were studied in mice. Agents were administered intraperitoneally in mice before the experiments for the evaluation of hypnotic activity (induced by sodium pentobarbital, 30 mg/kg, ip), anxiolytic activity (elevated plus maze test), locomotor activity (open field test) and motor coordination (Rotarod test). The aqueous extract reduced the locomotor activity dose dependently. At low doses, saffron showed a significant increase in the time on the open arms of the maze. When using the Rotarod method, the aqueous extract showed considerable effect on motor coordination of the mice. In the hypnotic test, only a dose of 0.56 g/kg of saffron increased the total sleep. Crocin showed no anxiolytic, hypnotic or myorelaxation effects. Safranal, in higher doses, 0.15 and 0.35 ml/kg, showed anxiolytic effects. Safranal increased the total sleep time dose dependently. This constituent at lower doses (0.05 and 0.15 ml/kg) decreased some locomotion activity parameters. Safranal demonstrated no effects on motor coordination. Based on the results, saffron aqueous extract and safranal showed anxiolytic and hypnotic effects [115].

Intragastric administration of 125–250 mg/kg bw of a 50% ethanol extract of the stigmas showed tranquillizing effect and potentiated the sedative effects of barbiturates in mice [116].

The anxiolytic properties of crocins was investgated in rodents via light/dark test. Crocins, at a dose which did not influence animals' motor activity (50 mg/kg), or diazepam (1.5 mg/kg), increased the rats latency to enter the dark compartment and prolonged the time spent in the lit chamber. Lower doses of crocin (15-30 mg/kg) did not modify animals behavior [117].

Antianxiety-like behavior of aqueous, ethanolic and acetonitrile *Crocus sativus* extracts have been investigated in forced-swimming stress in rats. Different doses of extracts (10, 30, 60 mg/kg) were injected intraperitoneally (ip) in a 9-day period, meanwhile, swimming stress was performed for 15 minutes in four sessions (days 3, 5, 7 and 9). The time performing the followings: immobility, swimming and struggling was measured. Moreover, free fatty acids, glucose, corticosterone and HSP70 were also measured. The outcomes demonstrated that saffron decreased stress significantly by prolonging immobility and decreasing the active behavior swimming, without much effect on struggling. The extracts also showed significant reduction in levels of the stress biomarkers. Acetonitrile was identified as the most effective extract in reducing anxiety. The saffron extracts probably proved anti-stress and sedative properties, partly due to distinct proportion and synergistic impact of the active constituents. On the other hand, crocin and safranal have anti-oxidant and anti-inflammatory powers that may aid to mediate this protective central impact[118].

The effects of saffron water extract and its constituent, safranal was studied on the behavioral and metabolic signs induced by electroshock stress in male Wistar. Animals were received intra-amygdala (1, 5, and 10 µg/rat) or intraperitoneal (1, 5, and 10 mg/kg) of the extract, safranal, or saline 5 or 30 min before stress induction. The results showed that stress elevated the corticosterone plasma concentration (115 nmol/l) in the control and intra-amygdala (1, 5, and 10 µg/rat)-treated groups but not in groups received extract or safranal (55 nmol/l) intraperitoneally (1, 5, and 10 mg/kg). Moreover, anorexia was reduced only in groups received the extract (1, 5, and 10 mg/kg) or safranal (1, 5, and 10 mg/kg) intraperitoneally (50 sec). Stress increased sniffing, rearing, locomotion, and coping time, which were decreased by intraperitoneal (1, 5, and 10 mg/kg) but not by intra-amygdala (1, 5, and 10 µg/rat) administration of saffron extract and safranal. The results revealed that saffron water extract and safranal had an important impact on the reduction of both metabolic and behavioral signs of stress in male rats [119].

Cynodon dactylon

The dried extracts of aerial parts of *Cynodon dactylon* were evaluated for CNS activities in mice. The ethanol extract of aerial parts of *Cynodon dactylon* (EECD) was found to cause significant depression in general behavioral profiles in mice. EECD also significantly potentiated the sleeping time in mice induced by standard pentobarbitone sodium, diazepam, and meprobamate in a dose dependant manner [120].

The effects of ethanol extract of aerial parts of *Cynodon dactylon* (EECD) were studied to investigate its CNS depressant pharmacological properties in the classical behavioral models (open-field, elevated plus maze-EPM, Rota-rod, and barbiturate-induced sleeping time) in mice. Extract was given in 50% propylene

glycol as a solvent, as a single dose of 50, 75 and 100mg/kg ip. No significant effect was evident on motor coordination of the animals in the rotarod test. On EPM, all the doses of EECD caused significant reduction in the time of permanence in the open arms. In addition, EECD increased the immobility time in the forced swimming test and potentiated pentobarbital-induced sleeping time in mice, confirmed a probable sedative and central depressant effect in the animals [121].

Cyperus rotuntdus

The ethanolic extract of *Cyperus rotundus* showed potent tranquilizing activity in many tests. It reduced the spontaneous motor activity, potentiated the pentobarbital narcosis and deranged the motor coordination and abolished the conditioned avoidance response in animals [122-123].

The behavioral studies on mice indicated CNS depressant activity of the ethanol extract of *Cyperus rotundus*. The ethanol extract of *Cyperus rotundus* significantly potentiated the sleeping time of mice induced by standard hypnotics (pentobarbitone sodium, diazepam, and meprobamate) in a dose dependent manner [124].

Four sesquiterpenes (beta-selinene, isocurcumenol, nootkatone and aristolone) and one triterpene (oleanolic acid) were isolated from the ethylacetate fraction of the rhizomes of *Cyperus rotundus* and tested for their ability to modulate gamma-aminobutyric acid ($GABA_A$)-benzodiazepine receptor function by radioligand binding assays using rat cerebrocortical membranes. Among these compounds, only isocurcumenol was found to inhibit [^{3}H]Ro15-1788 binding and enhance [^{3}H]flunitrazepam binding in the presence of GABA. The results suggested that isocurcumenol may serve as a benzodiazepine receptor agonist and allosterically modulated GABAergic neurotransmission via enhancement of endogenous receptor ligand binding [125].

***Datura* species**

25 g/kg of methanolic crude extract induced behavioural sleep patterns (EEG) similar to that of thiopental in rats[126].

Echium italicum

The anxiolytic and hypnotic effects of the aqueous and ethanolic extracts of aerial parts of E. italicum was evaluated in mice. Mice were administered the extracts intraperitoneally before the start of the experiments for evaluation of hypnotic activity (induced by sodium pentobarbital, 30 mg/kg, ip), anxiolytic activity (elevated plus-maze [EPM] test), locomotor activity (open field test), and motor coordination (rotarod test). The ethanolic and aqueous extracts of E. italicum, at doses of 1.2 and 2.1 g/kg, increased the percentage of time-spent and the percentage of arm entries in the open arms of the EPM and decreased the percentage of time-spent in the closed arms of the EPM. Both extracts decreased the pentobarbital-induced latency to sleep and significantly increased the total sleeping time induced by pentobarbital. Locomotor activity was affected by aqueous extracts and ethanolic extract (at higher doses). Both extracts showed no effect in the rotarod test. According to these results, both ethanolic and aqueous extracts of E. italicum showed anxiolytic and sedative activity but not muscle relaxant activity[127].

Equisetum arvense

Hydroalcoholic extract of *Equisetum arvense* (200 and 400 mg/kg) increased the sleeping time (46% and 74% respectively) in the barbiturate-induced sleeping time[128].

The effects of sedative, pre-anesthetic and anti-anxiety of Equisetum arvense with diazepam were studied in rats. The extract of Equisetum arvense was given at doses of (100,200,400 mg/kg , ip) and Diazepam with dose of(0.5 mg/kg , ip). The hydroalcoholic extract of *E. arvense* caused a significant increase in ketamine induced sleep and showed anxiolytic, sedative and preanesthetic effects at a dose of 200 mg/kg i.p[129].

Eschsholzia californica

A multicenter, double-blind, randomized, placebo-controlled study was carried out in general practice offices in Paris, France and the Paris area. Men and women (N = 264) with mild to moderate generalized anxiety disorder as diagnosed according to the DSMIII- R criteria participated. Patients received either 2 tablets of placebo or Sympathyl® (Laboratoire Innotech International, Arcueil, France) twice daily for 3 months. Sympathyl contains 75 mg of dry hydro-alcoholic extract of the flowering head of hawthorn, 20 mg of dry aqueous extract of California poppy, and 75 mg of elemental magnesium. Efficacy was assessed by change in Hamilton anxiety scale total and somatic scores, change in patient self-assessment, number and percentage of responsive subjects (reduction of at least 50% in Hamilton or self-assessment score) and the physician's clinical global impression. Treatment produced a rapid and progressive fall in anxiety. There was a significant

improvement in the total anxiety score (P = 0.005), somatic score (P = 0.054), and self-assessment (P = 0.005) in patients taking Sympathyl for 3 months[130].

The aqueous extract of *Eschsholzia californica* reduced the behavioural parameters measured in a familiar environment test in mice (novelty preference, locomotion and rearings in two compartments test) at doses above 100 mg/kg and in non-familiar environment tests (staircase test) at doses above 200 mg/kg. The aqueous extract of Eschsholzia californica at a dose a of 25 mg/kg, E. californica also possessed anxiolytic action since it produced an increase of the number of steps climbed by mice in the staircase test (anticonflict effect) and that of the time spent by animals in the lit box when they were confronted with the light/dark choice situation[131].

Foeniculum vulgare

The anxiolytic activity of the essential oil of *Foeniculum vulgare* (50, 100, and 200 and 400 mg/kg doses) was studied in mice using elevated plus maze (EPM), staircase test (SCT) and open field test (OFT). In EPM test, 100 and 200 mg/kg doses of the essential oil significantly increased percent number of entries and time spent in open arms compared to control. In SCT these doses also reduced rearing significantly compared to controls, while only the 200 mg/kg dose significantly increased number of squares crossed at the center in the OFT test[132].

The anxiolytic activity of ethanolic extracts of *Foeniculum vulgare* fruit was evaluated by elevated plus maze, rota rod, open field test, and hole board model in mices. The efficacy of extract (100-200mg/kg) was compared with standard anxiolytic drugs diazepam (1mg/kg). Extract administered animals showed exploratory behavior with all tests similar to diazepam. The results showed that the extract significantly increased the number of entries and time spent in the open arm in the elevated plus maze apparatus. In open field test, the extract showed significant increase in number of rearings, assisted rearing and number of square crossed[133].

The anxiolytic activity of the crude ethanolic extract of *Foeniculum vulgare*

was studied in albino mice by elevated plus-maze model. The extract at doses of 200 mg/kg and 400 mg/kg has been found to possess significant anti-anxiety activity on the tested experimental models. The extract (400 mg/kg) exhibited maximum anti-anxiety effect. At a higher dose the extract (400 mg/kg) showed increase number of entries and time spent in open arm of elevated plus-maze model. The effect produced by the extract was comparable to that of diazepam[134].

The anti-stress and memory-enhancing properties of F. vulgare boiling water extract (50, 100 and 200 mg/kg, orally) were studied in experimental rats. Urinary levels of vanillylmandelic acid (VMA) and ascorbic acid in rats were used to evaluate anti-stress activity. Conditioned avoidance response was measured in normal and scopolamine-induced amnesic rats to study the memory-enhancing effects. Lipid peroxidation inhibition assay in liver and brain homogenates of rats was used to evaluate antioxidant activity. Daily administration of F. vulgare extract (50, 100 and 200 mg/kg body weight) 1 h prior to induction of stress significantly ($p < 0.05$) altered the stress-induced urinary biochemical levels of VMA from 395.79 ± 11.23 to 347.12 ± 12.28, 311.21 ± 12.48 and 258.86 ± 10.26 μg/kg, respectively, in 24 h, as well as ascorbic acid excretion levels from 65.74 ± 9.42 to 78.59 ± 8.44, 108.41 ± 15.62 and 125.82 ± 16.94 μg/kg also within the same period, respectively. These changes occurred in a dose-dependent fashion, and the levels in the control groups were unchanged within the same period. The memory deficits induced by scopolamine (1mg/kg, ip) in rats was reversed by F. vulgare dose-dependently. The extract also exhibited potent antioxidant effect by inhibition of lipid peroxidation in both rat liver and brain homogenates to a greater extent than the standard antioxidant, ascorbic acid [135].

Helianthus annuus

The methanolic extract of *Helianthus annuus* seeds also caused moderate anxiolytic activity (light-dark box and elevated plus maze test). *H. annuus* showed moderate increase in the latency of entry into the light box with peak effect produced at the dose of 200 mg/kg (72±0.85 seconds) compared to control (34±5.63 seconds). In respect of latency of entry into the light box and number of entries, the values for *H. annuus* showed moderately significant anxiolytic effect at the dose of both 100mg/kg (63±0.62 seconds) and 200 mg/kg (72±0.85 seconds). *H. annuus* produced a significant increase in the time spent in the open arms with peak effect produced at the dose of 100 mg/kg (51±0.62 seconds) relative to control (30.23±0.62 seconds). In respect of entry into open arms, the extract at the dose of 100 mg/kg significantly ($p<0.05$) increased the number of entries compared to control. The number of entries into the closed arms was reduced by *H. annuus* at doses of 100 and 200 mg/kg[136].

Jasminum sambac

The anxiolytic and antidepressant activities of ethanolic extract of *Jasminum sambac* flowers were evaluated using elevated plus maze, actophotometer, froced swim test and tail suspension test in mice. The

ethanolic extracts of flowers of *J.Sambac* at a dose of 200 and 400mg/kg ip, significantly possessed antidepressant and anxiolytic activity[137].

The antistress activity of the methanolic extract of Jasminum sambac (MEJS) leaves was studied against swimming stress induced gastric ulceration in rats and swimming endurance test in mice. Swimming stress induced changes in Ulcer index and histopathology in rats were compared with the standard. The biochemical parameters such as Urea, Triglycerides, Cholesterol, Alkaline phosphatase, SGPT, SGOT etc were examined in stressed and treated groups of rats. MEJS at a dose of 100 mg/kg and 200 mg/kg po, exhibited good antistress effect in both tested models. MEJS reduced the incidence of gastric ulceration in stressed rats. It also prevented the biochemical changes induced by forced swimming stress such as increase in plasma alkaline phosphatase, SGPT, SGOT, Urea, Triglycerides and Cholesterol. The stress induced rise in cholesterol and urea levels were significantly lowered by the extract. Also, the stress induced rise in plasma enzyme levels of SGPT and SGOT were significantly reduced when treated with the methanolic extract of *Jasminum sambac* at 100mg/kg and 200mg/kg bw and was comparable with the standard drug Geriforte at 43mg/kg bw. The MEJS treated animals also showed an increase in swimming endurance time, which was almost comparable with that of standard drug[138].

Juglans regia

The anxiolytic effect of hydroalcoholic extract of *Juglans regia* fruit (200 and 400 mg/kg bw) was studied on the basis of effect on exploration behaviour and anxiety in elevated plus maze, zero maze, and light-dark model. *Juglans regia* extract produced significant effect on exploration and time spent in open area of elevated plus maze and zero maze. Extract also increased time spent in lighten area in light and dark model. Increase in number of head twitches was also observed at selected doses[139].

IV. Plants affected locomotion activity:

Alhagi maurorum

Alhagi maurorum decreased the locomotion activity of the animals and skeletal muscle relaxation. Exposure of the frog's rectus abdomen is muscle to the extract in a concentration of 4 μg/ml bathing fluid for 5min antagonize ACh (3 μg/ml)-induced contraction by 70 ± 2.1% (N = 4). When the dose of ACh was increased up to 8 μg/ml in presence of the extract blockade, it did not reverse completely the blockade. The maximum reversal of antagonism was 27.7, suggesting that the extract blocked the action of ACh in a non-competitive manner. Intraperitoneal administration of the ethanolic extract (EE) of *Alhagi maurorum* powdered roots into conscious mice in doses of 1.6 g/kg produced mild sedation. The extract also decreased the locomotion activity of the animals and skeletal muscle relaxation suggesting an action at the skeletal muscles neuromuscular junctions [140].

Anthemis nobelis

In mice, apigenin had a clear affinity for central benzodiazepine receptors. Apigenin competitively inhibited the binding of flunitrazepam, a benzodiazepine, but had no effect on muscarinic receptors, alpha 1-adrenoceptors, or the binding of muscimol to GABA receptors. Apigenin had clear anxiolytic activity in mice without incidence of sedation or muscle relaxation effects at doses similar to those used for classical benzodiazepines; no anticonvulsant action was detected. Increasing dosages produced mild sedation and a reduction in ambulatory locomotor activity [81-82,141-142].

Arundo donax

Bufotenidine isolated from *Arundo donax* showed neuromuscular blocking activity [143].

Benincasa hispida

The anxiolytic effects of alcoholic extract of *B. hispida* were evaluated in mice using elevated plus maze and light-dark transition test and spontaneous motor activity measured by actophotometer. The extract possessed anxiolytic activity but was not able to modify the spontaneous motor activity measured in actophotometer [144].

However, the methanolic extract of fruit of *Benincasa hispida* caused reduction in spontaneous motor activity with no muscle relaxant activity [145].

Caesalpinia crista

The effects of *Caesalpinia crista* extract on gallamine-induced relaxation in rat tibial muscle contractility were studied via measurement of isometric-tension-anesthetized, 10-12-week-old, male rats. *Caesalpinia crista* extract administered intravenously (iv) increased twitch contractions in a dose-dependent manner. The ED_{50} value was 2.75 x 10-4 g/kg bw. Treatment with *Caesalpinia crista* extract or neostigmine,

however, reversed the relaxation induced by either gallamine or puff adder venom. The authors concluded that *Caesalpinia crista* extract stimulates the muscle contractile activity via activation of the cholinergic mechanism[146].

Carthamus tinctorius

Subcutaneous administration of 1–10 g/kg bw of an aqueous or 50% methanol extract of the flowers had central nervous system depressant effects and relaxed skeletal muscles in mice [147].

***Datura* species**

The neuropsychopharmacological effects of aqueous extracts of leaves and seeds of *D. fastuosa*, were studied in rat and mice . The leaf and seed extracts at doses of 400 and 800 mg/kg increased motor activity, reduced slightly the duration of barbituric sleeping, antagonized catalepsy and ptosis induced by haloperidol and the immobility induced by forced swimming. The results also showed that, *D. fastuosa* has some antidepressant profile at low doses[148].

Equisetum arvense

Ethanolic extract (100 mg/kg) prolonged the ketamine-induced total sleeping time and decreased the locomotor activity in mice[149].

Fumaria officinalis

The muscle relaxant and sedative activities of ethanolic extract of *Fumaria officinalis* were evaluated in experimental animal models. *Fumaria officinalis* (FO) (at 100,200 and 500 mg/kg body weight, ip) was evaluated for muscle relaxants activity by using Rota rod, Traction test and fall off time. The results revealed significant ($p< 0.001$) and dose dependent muscle relaxant and sedative potentiating effects of ethanolic extract of *Fumaria officinalis*, it demonstrated its depressant action on the central nervous system[150].

Hibiscus sabdariffa

The neuropharmacological effects of the aqueous extract of Hibiscus sabdariffa (HS) calyx were studied in rodents. HS (100, 200 and 400 mg/kg, i.p.) caused a remarkable dose-dependent decrease in spontaneous motor activity in mice [151].

V. Plant beneficial in Parkinson's disease:

Antirrhinum majus

Aurones belong to the family of flavonoids, structurally isomers of flavones, were synthesied in *Antirrhinum majus*. Aurones and extracts comprising them were useful in the prophylactic and/or therapeutic treatment of an animal (including a human) with a phosphodiesterase (PDE) dependent disease or condition of the central nervous system. Among the diseases and conditions of the nervous system to be treated prophylactically or therapeutically, neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, age related dementia or dementia in general, neurological trauma including brain or central nervous system trauma, depression, anxiety, psychosis, cognitive dysfunction, mental dysfuntion, learning and memory disorders, and ischemia of the central and/or peripheral nervous systems [152].

Bacopa monnieri

Bacopa monnieri, in pharmacological Caenorhabditis elegans models of Parkinson's, reduced alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent[153].

Carthamus tinctorius

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 [154].
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 vitroresults 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 [155].

Cuminum cyminum

The inhibitory effects of the *Cuminum cyminum* essential oil on the fibrillation of α-SN, which was a critical process in the pathophysiology of several neurodegenerative diseases, especially Parkinson's disease, was investigated. Analysis of different fractions from the total extract, identified cuminaldehyde as the active compound involved in the antifibrillation activity. In comparison with baicalein, a well-known inhibitor of α-SN fibrillation, cuminaldehyde showed the same activity in some aspects and a different activity on other parameters influencing α-SN fibrillation. The presence of spermidine, an α-SN fibrillation inducer, dominantly enforced the inhibitory effects of cuminaldehyde even more intensively than baicalein. Furthermore, the results from experiments using preformed fibrils and monobromobimane-labeled monomeric protein also suggested that cuminaldehyde prevents α-SN fibrillation even in the presence of seeds, having no disaggregating impact on the preformed fibrils. Structural studies showed that cuminaldehyde stalls protein assembly into β-structural fibrils, which might be achieved by the interaction with amine groups through its aldehyde group as a Schiff base reaction. This assumption was supported by FITC labeling efficiency assay. In addition, cytotoxicity assays on PC12 cells showed that cuminaldehyde is a nontoxic compound, treatment with cuminaldehyde throughout α-SN fibrillation showed no toxic effects on the cells [29, 156].

Cyperus rotuntdus

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 [157].

Geum urbanum

The presence of Lewy bodies and Lewy neurites is a major pathological hallmark of Parkinson's disease and is hypothesized to be linked to disease development. . Lewy bodies and Lewy neurites primarily consist of fibrillated α-Synuclein. The inhibitory activity of an ethanolic extract of Geum urbanum against α-Synuclein fibrillation was studied. The anti-fibrillation and anti-aggregation activities of the plant extract were monitored by thioflavin T fibrillation assays and size exclusion chromatography, while structural changes were followed by circular dichroism, Fourier transform infrared spectroscopy, intrinsic fluorescence, small angle X-ray scattering and electron microscopy. Geum urbanum inhibited α-Synuclein fibrillation in a concentration dependent way, and to partly disintegrate preformed α-Synuclein fibrils. Based on the structural changes of α-Synuclein in the presence of extract, It appeared that Geum urbanum delayed α-Synuclein fibrillation either by reducing the fibrillation ability of one or more of the aggregation prone intermediates or by directing α-Synuclein aggregation towards a non-fibrillar state [158].

Hyoscyamus niger

The neuroprotective potential, of petroleum ether and aqueous methanol extracts of *Hyoscyamus niger* seeds was evaluated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson disease in 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 [159].

Juglans regia

The neuro protective efficacy of dietary supplementation of walnut (6 %) for 28 days was examined in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neurodegeneration in a Mouse model of Parkinson's disease (20 mg/kg bw/day, ip) for 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 in MPTP 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[160].

Juniperus communis

The effect of methanolic extract of Juniperus communis (MEJC) leaves on reserpine induced catalepsy was studied in rats. Catalepsy was induced by intra administration of reserpine (2.5 mg/kg, ip). The methanolic extract at 100 and 200 mg/kg, ip were screened for its efficacy against reserpine induced catalepsy in rats. The MEJC extract reduced catalepsy significantly ($p<0.001$) as compared to the reserpine treated rats, maximum reduction was observed at a dose of 200 mg/kg. Accordingly, J. Communis possessed a therapeutic effect against Parkinson's disease in reserpine induced animal Parkinson's disease models[161].

The neuroprotective activity of methanolic extrct of J. communis (MEJC) was evaluated in chlorpromazine (CPZ) induced Parkinson's model in rats (100 and 200mg/kg, ip). The neuroprotective activity was evaluated using behavior parameters like catalepsy (bar test), muscle rigidity (rot rod test), and locomotor activity (actophotometer) and its effect on biochemical parameters (TBARS, GSH, nitrite, and total protein) in rats brain. J. communis possessed significant (P <0.001) neuroprotective effect against CPZ induced Parkinson's like symptoms[162].

VI. Plants beneficial in Alzheimer's disease and memory deficits:

Alzheimer's disease:

Antirrhinum majus

Aurones and extracts comprising them were useful in the prophylactic and/or therapeutic treatment of an animal (including a human) with a phosphodiesterase (PDE) dependent disease or condition of the central nervous system. Among the diseases and conditions of the nervous system to be treated prophylactically or therapeutically, neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, age related dementia or dementia in general, neurological trauma including brain or central nervous system trauma, depression, anxiety, psychosis, cognitive dysfunction, mental dysfuntion, learning and memory disorders, and ischemia of the central and/or peripheral nervous systems [152].

Bacopa monniera

The effect of sub-chronic administration (14 days) of a standardized extract of *Bacopa monniera* (BM) (bacoside A content 82.0 ± 0.5%) on two animal models of Alzheimer's disease, induced by administration of colchicine and by lesioning of nucleus basalis magnocellularis (nbm) with ibotenic acid. Lesioning with colchicine or ibotenic acid induced marked deficits in the retention of active avoidance learning, which was evident on day 7, after lesioning, and increased progressively by day 14. Subchronic administration of BM reduced the magnitude of memory deficits induced by both colchicine and ibotenic acid, which was significant at days 7 and 14 with the higher dose, 10 mg/kg, orally, and on day 14 only with the lower dose, 5 mg/kg orally, of BM. BM (10 mg/kg,orally) reversed colchicine-induced reduction in frontal cortex and hippocampal Ach, ChAT activity and MCR binding. The effect of the lower dose of BM (5 mg/kg, orally) was evident only after 14 days[163].

Benincasa hispida

The chronic treatment with the aqueous extract of *Benincasa hispida* pulp (400mg/kg bw) appeared beneficial in the management of colchicines-induced rat model of Alzheimer's disease. It was also increased antioxidants in different brain areas and increased the number of correct choices out of 10 daily trials and decreased latency time dose dependently [164-165].

Caesalpinia crista

Amyloid beta (A beta) is the major etiological factor implicated in Alzheimer's disease. The ability of *Caesalpinia crista* leaf aqueous extract was studied on the prevention of (i) the formation of oligomers and aggregates from monomers (Phase I: A beta(42) + extract co-incubation); (ii) the formation of fibrils from oligomers (Phase II: extract added after oligomers formation); and (iii) dis-aggregation of pre-formed fibrils (Phase III: aqueous extract added to matured fibrils and incubated for 9 days). The aggregation kinetics was

monitored using thioflavin-T assay and transmission electron microscopy. The results showed that *Caesalpinia crista* aqueous extract was able to inhibit the A beta(42) aggregation from monomers and oligomers and also able to dis-aggregate the pre-formed fibrils [166].

Carthamus tinctorius

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 [145, 167].

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 [168].

Cistanche tubulosa

The ameliorating effects of *Cistanche tubulosa* extract which was quantified with three phenylpropanoid glycosides was studied in Alzheimer's disease (AD)-like rat model. Amyloid β peptide 1-42 (Aβ 1-42) intracisternally infused rats by osmotic pump was used as an AD-like rat model. The major pathological makers were measured including Aβ 1-42 immunohistochemical stain, behavioral tests (inhibitory avoidance task and Morris water maze) and central neurotransmitter functions. Aβ 1-42 caused cognitive deficits, increased amyloid deposition and acetylcholine esterase activities, and decreased the levels of brain's acetylcholine and dopamine. Daily administration of *Cistanche tubulosa* extract throughout Aβ 1-42 infusion periods ameliorated the cognitive deficits, decreased amyloid deposition and reversed cholinergic and hippocampal dopaminergic dysfunction caused by Aβ 1-42 [169].

The efficacy and safety of *Cistanche tubulosa* glycoside capsules (CTG capsule, Memoregain®) for treating Alzheimer's disease (AD) were studied clinically. A total of 18 patients with AD administered with Memoregain® for 48 weeks were assessed for drug efficacy by Alzheimer's disease assessment scale–cognitive subscale (ADAS-cog), mini-mental state examination (MMSE), activities of daily living (ADLs), blessed behavioral scale, and clinical global impression (CGI) scales. The MMSE score was 14.78 ± 2.51 at baseline and 14.06 ± 4.26 at study completion. While changes in ADAS-cog score before and after 48 weeks of treatment were statistically insignificant, the score improved, deteriorated, and remained unchanged in 10, 7, and 1 patients, respectively. The ADL and CGI scores showed no significant difference from baseline. All adverse reactions were mild. After Memoregain® treatment, patients with AD showed no obvious aggravation of cognitive function, independent living ability, and overall conditions but were stable throughout the study. Comparison with other long-term medications, acetylcholinesterase inhibitors suggests that Memoregain® has a potential to be a possible treatment option for mild to moderate AD [170-171].

The body of *Cistanche tubulosa* (Schenk.) Wight, was used to make a medicinal preparation containing phenylethanoid glycosides and comprising 10-70% of echinacoside and 1-40% of acteoside by weight of the preparation. The medicinal preparation was used effectively in prevention of senile dementia, and inhibition of aggregation of blood platelets [172].

Clitoria ternatea

Seeds and leaves of *Clitoria ternatea* have been widely used as brain tonic and believed to promote memory and intelligence. The activity of *Clitoria ternatea* in Alzheimer's disease was studied to investigate its efficacy and to identify the major bioactive constituent attributing the activity. The result showed that the aqueous extract of *Clitoria ternatea* was beneficial in Alzheimer's disease through many mechanisms. The isolated compounds may act as a lead compounds for identifying new derivatives which could use for improving memory [173-174].

Colchicum balansae

Methanol extracts of the seeds of *Colchicum balansae* were investigated for their *in vitro* cholinesterase (AChE and BChE) inhibitory activity at 200 µg/ ml, using ELISA microplate assay. Acetylcholinesterase inhibitory activity possessed by the methanolic extracts of *Colchicum balansae* seeds extract (200µg/ml) was 10.90 ±1.17% and BChE inhibitory activity was 44.22 ±2.46% [175-176].

Many authors mentioned that Acetylcholinesterase inhibitors are the most effective approach to treat the cognitive symptoms of Alzheimer's disease. Althoudh acetylcholinesterase inhibitors was the most widely used medication in Alzheimer's disease treatment, but some report propound that acetylcholinesterase inhibitors have inclement side effects such as anorexia, diarrhoea, fatigue, nausea, muscle cramps as well as gastrointestinal, cardiorespiratory, genitourinary and sleep disturbances. Accordingly, medical field search for new acetylcholinesterase inhibitors with higher efficacy from natural sources. *Colchicum balansae* is one of the promising sources [175-177].

Coriandrum sativum

The effects of inhaled coriander volatile oil (1% and 3%, daily, for 21days) on spatial memory performance were assessed in an Aβ(1-42) rat model of Alzheimer's disease. The Aβ(1-42)-treated rats exhibited the following: decrease of spontaneous alternations percentage within Y-maze task and increase of working memory errors, reference memory errors and time taken to consume all five baits within radial arm maze task. Exposure to coriander volatile oil significantly improved these parameters, suggesting positive effects on spatial memory formation. Assessments of oxidative stress markers in the hippocampal tissue of Aβ(1-42)-treated rats showed a significant increase of superoxide dismutase (SOD), lactate dehydrogenase (LDH) and a decrease of glutathione peroxidase (GPX) specific activities along with an elevation of malondialdehyde (MDA) level. Coriander volatile oil significantly decreased SOD and LDH specific activities, increased GPX specific activity and attenuated the increased MDA level. Also, DNA cleavage patterns were absent in the coriander rats, thus suggesting antiapoptotic activity of the volatile oil. Accordingly, the exposure to coriander volatile oil ameliorated Aβ(1-42)-induced spatial memory impairment by attenuation of the oxidative stress in the rat hippocampus [178].

Cressa cretica

The effects of *Cressa cretica* was evaluated in learning and memory in mice. Elevated plus maze and passive avoidance paradigm were utilized to test learning and memory. Two doses (200 and 400 mg/kg, po) of ethanolic extract were administered for 28 successive days in separate group of animals. The dose of 400 mg/kg po, of *Cressa cretica* extract (CCE) significantly improved learning and memory of mice. Furthermore, this dose significantly reversed the amnesia induced by scopolamine (0.4 mg/kg, ip). To find out the mechanism by which CCE exerted nootropic activity, the effect of CCE on whole brain AChE activity was also estimated. CCE decreased whole brain acetyl cholinesterase activity and reduced whole brain MDA and NO levels. The antioxidant properties and the presence of flavonoids in *Cressa cretica* may be contributing to memory enhancement effect. Accordigly, *Cressa cretica* was a potent candidate for enhancing learning and memory and it would be beneficial for the treatment of amnesia and Alzheimer's disease [179-181].

Crocus sativus

Alzheimer's disease was characterized pathologically by deposition of amyloid beta-peptide (Abeta) fibrils. Oxidation was thought to promote Abeta fibril formation and deposition. To identify agents inhibiting the pathogenesis of Alzheimer's disease, the antioxidant properties of *extract* of Crocus sativus stigmas and its effect on Abeta(1-40) fibrillogenesis was investigated in vtro. The antioxidant properties were determined by measuring the ferric-reducing antioxidant power and Trolox-equivalent antioxidant capacity, while its effects on Abeta-aggregation and fibrillogenesis were studied by thioflavine T-based fluorescence assay and by DNA binding shift assay. The water: methanol (50:50, v/v) *extract* of Crocus sativus stigmas possessed good antioxidant properties, higher than those of tomatoes and carrots, and inhibited Abeta fibrillogenesis in a concentration and time-dependent manner. The main carotenoid constituent (trans-crocin-4) the digentibiosyl ester of crocetin, inhibited Abeta fibrillogenesis at lower concentrations than dimethylcrocetin, revealing that the action of the carotenoid was enhanced by the presence of the sugars. The result suggest the possible use of Crocus sativus stigma constituents for inhibition of aggregation and deposition of Abeta in the human brain [182].

Inhibitors of acetylcholine breakdown by acetylcholinesterase (AChE) constituted the main therapeutic modality for Alzheimer's disease. The inhibition of AChE activity of saffron *extract* and its constituents was studied by in vitro enzymatic and molecular docking studies. Saffron *extract* showed moderate AChE inhibitory activity (up to 30%), but IC_{50} values of crocetin, dimethylcrocetin, and safranal were 96.33, 107.1, and 21.09 µM, respectively. Kinetic analysis showed mixed-type inhibition, which was verified by in silico docking

studies. Safranal interacted only with the binding site of the AChE, but crocetin and dimethylcrocetin bind simultaneously to the catalytic and peripheral anionic sites [183].

The efficacy of Crocus sativus *was studied* in the treatment of patients with mild-to-moderate Alzheimer's disease. Fifty-four Persian adults, 55 years of age or older were participated in a 22-week, double-blind study of parallel groups of patients with AD. The main efficacy measures were the change in the Alzheimer's Disease Assessment Scale-cognitive subscale and Clinical Dementia Rating Scale-Sums of Boxes scores compared with baseline. Adverse events (AEs). Participants were randomly assigned to receive a capsule saffron 30 mg/day (15 mg twice per day) or donepezil 10 mg/day (5 mg twice per day). Saffron at this dose was found to be effective similar to donepezil in the treatment of mild-to-moderate AD after 22 weeks. The frequency of AEs was similar between saffron *extract* and donepezil groups with the exception of vomiting, which occurred significantly more frequently in the donepezil group [184].

Cupressus sempervirens

The dichloromethane, acetone, ethyl acetate, and methanol extracts of the cones and leaves of *Cupressus sempervirens* var. *horizantalis* (CSH) and var. *pyramidalis* (CSP) were screened for their inhibitory activity against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and tyrosinase (TYRO). The extracts displayed weak to moderate cholinesterase inhibition at 200 µg/ml. The cone dichloromethane extract of CSP showed the highest inhibition (36.10±1.45%) against AChE, while the best inhibition (40.01±0.77%) against BChE was caused by the leaf acetone extract of CSH [185].

The antiacethylcholinesterase study of *Cupressus sempervirens* essential oil was also investigated. It showed that essential oil inhibitory concentration (IC_{50}) was 0.2837 ± 0.0115 mg/ml [186-187].

Cymbopogon schoenanthus

The acetylcholinesterase inhibitory activity of the essential oils from fresh leaves, dried leaves and roots of *Cymbopogon schoenanthus* was investigated. The greatest acetylcholinesterase inhibitory activity (IC_{50} = 0.26 ± 0.03 mg/ ml) was exhibited by the essential oil of the fresh leaves from the mountain region in southern Tunisia[188].

Aqueous extract, proanthocyanidin rich extract, and organic extracts of *Cymbopogon schoenanthus* shoots from three different locations in south Tunisia were screened for acetylcholinesterase inhibitory activity. The greatest acetylcholinesterase inhibitory activity (IC_{50} =0.23±0.04mg/ml) was exhibited by the ethyl acetate and methanol extracts of the plants collected from the mountainous region in Tunisia [27,189].

Daucus carota

The effects of *D. carota* seeds was evaluated in memory in rats. The ethanolic extract of *Daucus carota* (DCE) was administered orally in three doses (100, 200 and 400 mg/kg) for seven successive days to different groups of young and aged rats. Elevated plus-maze, Hebb-Williams maze and hexagonal swimming pool were used as exteroceptive behavioral models for testing memory. Diazepam-, scopolamine- and aging-induced amnesia were used as interoceptive behavioral models. DCE (200 and 400 mg/kg, po) induced significant improvement in memory of young and aged rats in elevated plus maze, Hebb Williams maze and hexagonal swimming pool. It also reversed the amnesia induced by scopolamine (0.4 mg/kg, ip) and diazepam (1mg/kg, ip). The results clearly indicated that *D. carota* seeds is a promising therapy to improve memory especially in management of Alzheimer patients[(57)]. The seeds which contain choline, and have been reported to inhibit brain cholinesterase activity, with a possibility to elevate the brain acetylcholine levels via increased synthesis of acetylcholine, which beneficial in cognitive dysfunctions[190-191].

Foeniculum vulgare

The nootropic and anticholinesterase potential of *Foeniculum vulgare* was studied in mice. Methanolic extract of the whole plant of *F. vulgare* administered for eight successive days ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging- induced memory deficits in mice. The passive avoidance paradigm was used as exteroceptive behavioral model for assessing memory. *F. vulgare* extract increased step-down latency and acetylcholinesterase inhibition in mice significantly. The authors postulated that *F. vulgare* can be employed in treatment of cognitive disorders such as dementia and Alzheimer's disease[192].

Fumaria officinalis

F. officinalis appeared the most potent AChE acetylcholinesterase inhibitors among many *Fumaria* species, on a plant dry weight basis (IC50 = 4.7 ±0.2 mg dry weight/ml), acetylcholinesterase inhibitory effects were correlated to the amount of protopine contained in 1 g of complex alkaloid islated from the species[193].

Isoquinoline alkaloids isolated from aerial parts of *Fumaria officinalis* were evaluated for their biological activities related to Alzheimer's disease. Parfumidine and sinactine exhibited potent prolyl oligopeptidase (POP) inhibition activities (IC_{50} 99±5 and 53±2 μM, respectively)[194].

Fumaria parviflora

The chloroform: methanol [1:1] extracts of a number of the plant species belonging to eight families, including *Fumaria parviflora*, were screened for their nticholinesterase activity on acetyl cholinesterase [AChE] and butyrylcholinesterase [BChE] enzymes by *in vitro* at 10 microg/ml and 1 mg/ml concentrations. Among the screened extracts, all of the Fumaria extracts displayed highly potent inhibition against both of the enzymes at 1 mg/ml concentration compared to the standard [195].

Glycyrrhiza glabra

The deposition of senile plaque that is contributed mainly by amyloid-β (Aβ), whose production is initiated by beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) is one of the typical hallmarks of Alzheimer's disease. Inhibition of BACE1 is thereby is an attractive strategy for anti- Alzheimer's disease drug discovery. The natural product 2,2′,4′-trihydroxychalcone (TDC) from Glycyrrhiza glabra functioned as a specific non-competitive inhibitor against BACE1 enzyme, and potently repressed β-cleavage of APP and production of Aβ in human embryo kidney cells. The amelioration ability of this compound against the in vivo memory impairment was further evaluated by APP-PS1 double transgenic mice model. 9 mg/kg/day of TDC decreased Aβ production and Aβ plaque formation, and efficiently improve the memory impairment based on Morris water maze test[196].

Gossypium herbaceam

The acetylcholinesterase (AChE) inhibition of a standardized extract from the flowers of the *Gossypium herbaceam* (GHE) as well as the protective effects to PC12 cells against cytotoxicity induced by tertiary butyl hydroperoxide (tBHP) were investigated using in vitro assays. The results revealed that GHE exhibited certain activities against AChE and also is an efficient free radical scavenger, which may be helpful in preventing or alleviating patients suffering from Alzheimer's disease[197].

***Haplophyllum* species**

The oil showed weakly acetylcholinesterase (AChE) inhibitory activity, compared to standard substances, whereas no inhibition on butyrylcholinesterase (BuChE) activity was observed[(51)]. The inhibitory activity of acetyl cholinestrase was mainly accumulated in the chloforom and ethyl acetate fractions of different parts extracts of H. tuberculatum. The most active was the stem ethyl acetate fraction with an inhibitory effect of 79% and IC_{50} of 0.45 μg/ml. Other fractions possessed an inhibitory effect at arrange between 70 – 77%[76, 198].

Hibiscus rosa sinensis

An aqueous extract of *Hibiscus rosa sinensis* showed 62.02%±0.03 (SEM) inhibitory activity against AChE and 57.83%±0.05 (SEM) inhibitory activity against BUChE enzymes respectively. Accordingly, *Hibiscus rosa sinensis* could be useful in improving memory[199].

Juglans regia

In vitro neuroprotective effects of the leaf and fruit extracts of *Juglans regia* were studied through enzymes linked to Alzheimer's disease and antioxidant activity. Extracts of *J. regia* fruits and leaves exhibited low inhibition of butyrylcholinesterase, and it possessed no significant effect on acetylcholinesterase[200].

Juniperus communis

The effects of inhaled juniper volatile oil (1% and 3%, daily, for 21 days) on spatial memory performance were assessed in an Aβ(1-42) rat model of Alzheimer's disease. The Aβ(1-42)-treated rats exhibited decrease of spontaneous alternations percentage within Y-maze task and increase of working memory and reference memory errors within radial arm maze task[201].

Memory enhancing effects:

Anchusa italica

Oral administration of Abnormal Savda Munsiq (ASMq) which contained *Anchusa italica*, also found to exert a memory-enhancing effect in the chronic stressed mice induced by electric foot-shock. The memory improvement of the stressed mice was shown by anincrease of the latency time in the step-through test and the

decrease of the latency time in the Y-maze test. Treatment with ASMq induced significant decrease the serum levels of adrenocorticotropic hormone, corticosterone and *β*-endorphin as well as the brain and serum level of norepinephrine. Furthermore, ASMq was able to significantly reverse the chronic stress by decreasing the brain and serum levels of the monoamine neurotransmitters dopamine, 5-hydroxytryptamine and 3, 4-dihydroxyphenylalanine [202].

Bacopa monniera

Memory deficits following cholinergic blockade by scopolamine were reversed by Bacopa treatment. Bacopa improved memory functioning in cognitively intact cohorts, with Pycnogenol improving working memory[203].

Benzodiazepines are known to produce amnesia by the involvement of GABAergic system and by the interference of long term potentiation. The behavioral study showed that *Bacopa monniera* significantly reversed the diazepam induced amnesia [204].

Bacopa administration with phenytoin significantly reversed phenytoin-induced cognitive impairment, as noted by improved acquisition and retention of memory [205].

A clinical trial was carried out to assess the effects of 12-weeks administration of *Bacopa monnieri* (300mg/day) on memory performance in people over the age of 55-years.Bacopa significantly improved memory acquisition and retention in older persons [206].

Significant cognitive enhancing benefits have been demonstrated with chronic administration of Bacopa extracts. A double-blind, placebo-controlled, 12-week trial utilizing the same patient selection criteria and the same dose of Bacopa extract (300 mg daily) containing 55% combined bacosides, was carried out. Forty-six healthy volunteers (ages 18-60) were randomly and evenly divided into treatment and placebo groups. The same series of tests administered in the acute dosage trial were administered at baseline, five, and 12 weeks after treatment began. At the end of the 12-week study, results indicated a significant improvement in verbal learning, memory consolidation, and speed of early information processing in the treatment group compared to placebo. These effects were not observed at baseline or at five weeks[207].

However , in a double-blind randomized, placebo control study performed on 76 adults aged between 40 and 65 years, in which various memory functions were tested and levels of anxiety was measured, the rate of learning was unaffected by *Bacopa monnieri* suggesting that *Bacopa monnieri* decreases the rate of forgetting of newly acquired information. Tasks assessing attention, verbal and visual short-term memory and the retrieval of pre-experimental knowledge were unaffected. Questionnaire measures of everyday memory function and anxiety levels were also unaffected [208].

Bellis perennis

The effects of aqueous extract of flowers from *Bellis perennis* on anxiety-like behavior and memory in Wistar rats were tested. *Bellis perennis (*20 and 60 mg/kg) administrated rats, spent more time at the center, showed less mobility and velocity. In the elevated plus maze, the high dose of *Bellis perennis* administrated rats spent more time in the open arms, spent less time in the closed arms, were less mobile, were slower and rotated less frequently. In the Morris water maze, the high dose of *Bellis perennis* administrated rats spent more of the time to find the platform. In conclusion, *Bellis perennis* may produce biphasic effects on both anxiety-like behaviour and learning performance of the rats[209].

Brassica nigra

The antiepileptic activity of methanolic extract of *Brassica nigra* seeds was investigated on maximal electroshock induced seizures (MES), Pentylene tetrazole (PTZ), Picrotoxin (PIC) and biccuculine induced seizures in mice. It was found that the extract (200 and 400 mg/kg, orally), significantly prolonged the onset of tonic seizures and reduced the duration of incidence of seizures in PTZ, PIC and biccuculine induced seizure models, while in MES model, the extract showed significant effect in abolishing tonic hind limb extensions by inhibiting voltage dependant Na+ channels or by blocking glutaminergic excitation mediated by the N-methyl-D-aspartate (NMDA) receptor [9, 210].

The anti-epileptic effect of the methanolic extract of *Brassica nigra* seeds (75, 150 and 300 mg/Kg; ip) was evaluated in pentylentetrazole (PTZ) - induced kindling in mice. The methanolic extract of *Brassica nigra* seed reduced the intensity and duration of seizure. In addition, the *Brassica nigra* extract increased the SOD and NO levels and decreased the MDA level in the brain tissues[211].

Bryophyllum calycinum

The methanolic extract of *Bryophyllum calycinum* Salisb showed neuro-pharmacological effects in experimental animals (rats and mice). The fraction produced alteration of behavior pattern, caused dose-dependent potentiation of pentobarbitone sleeping time and had significant analgesic activity and possesses a

potent CNS depressant action. The saline leaf extract of *Bryophyllum calycinum* Salisb produced a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis, reduction of exploratory activities in the head-dip and evasion tests. Moreover, a dose-dependent muscle in-coordination was observed in the inclined screen, traction and climbing tests in mice. The saline leaf extract produced a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis, reduction of exploratory activities in the head-dip and evasion tests and a dose-dependent muscle incoordination in the inclined screen, traction and climbing tests[98-100].

The CH_2Cl_2/CH_3OH extract reduced seizures induced by pentylenetetrazol, strychnine sulphate and thiosemicarbazide and increases in the latency period of seizures and reduced the duration of seizures induced by the three convulsive agents[99, 212-213].

Caesalpinia crista

The dried seed kernels of *Ceasalpinia crista*aqueous extract was examined as learning and memory enhancer. The memory retention in mice treated with 50mg/kg aqueous extract of dried seed kernels of *Caesalpinia crista* against scopolamine induced amnesia was found to be 33.09 % in radial arm maze task performance. However, the memory retention increased to 45.29% in mice treated with 150mg/kg (iv) of the same extract. Accordingly, the authors suggested that the extract could be beneficial to improve cognition in disorders like dementia and various neurodegenerative disorders [214].

Cistanche tubulosa

The improvement of learning ability and consolidation of *Cistanche tubulosa* extract was carried out with a step down test in mice. In this method, a platform (safe area) is located on an electric wire with 36 V current and mice's learning ability and consolidation were evaluated by the time they spend on the platform and the number of electronic shocks they received. Scopolamine (which may retard learning ability) was administered before the training started, and sodium nitrite (a drug to inhibit the synthesis of protein involved in the formation of memory by inducing oxygen deficit in the brain) was administered after the training in order to induce learning/memory disorder. As a result, the safe area time (latency) and the number of errors (frequency that mice hit by electronic shocks) were significantly better in the *Cistanche tubulosa* extract administration group as compared to the memory consolidation dysfunction model group. *Cistanche tubulosa* extract exerted stronger activity than piracetam, a pharmaceutical agent to activate energy metabolism of brain cells. According to these results, *Cistanche tubulosa* extract significantly helped the brain to recover from scopolamine-induced learning disorder and sodium nitrite-induced memory consolidation dysfunction and it improved the learning ability and formation of memory of brain [215].

On the other hand, water maze test was carried out to evaluate the memory recall ability of mice. Training was conducted to create memory in mice on the routes of water maze. *Cistanche tubulosa* extract (50-400 mg/kg) were orally administered to mice every day throughout the training period, four weeks. On the last day of the training, 30% ethanol was given to mice to induce memory loss (failing to recall memorized information). The mice in group consuming *Cistanche tubulosa* extract required shorter time to arrive destination compared to control. The rate of error was significantly lower in group consuming *Cistanche tubulosa* extract. *Cistanche tubulosa* demonstrated stronger activity than piraceetam. Accordingly, *Cistanche tubulosa* extract improved the ability to elicit or recall memorized information [216].

Citrus limon

The effect of *Citrus limon* on memory of mice was studied using Harvard Panlab Passive Avoidance response apparatus controlled through LE2708 Programmer. Passive avoidance was fear-motivated tests used to assess short or long-term memory of small animals, which measures latency to enter into the black compartment. Animals with *Citrus limon* treatment showed significant increase in latency to enter into the black compartment after 3 and 24 hours than control [217].

Clitoria ternatea

Shankhpushpi, a well-known drug in Ayurveda, is extensively used for different central nervous system (CNS) effects especially memory enhancement. Different plants were used under the name shankhpushpi in different regions of India, leading to an uncertainty regarding its true source. Plants commonly used under the name shankhpushpi are: *Convolvulus pluricaulis* Chois., *Evolvulus alsinoides* Linn., both from Convolvulaceae, and *Clitoria ternatea* Linn. (Leguminosae). The memory-enhancing activity of these three plants was investigated. Anxiolytic, antidepressant and CNS-depressant activities of these three plants were also evaluated and compared. The nootropic activity of the aqueous methanol extract of each plant was tested using elevated plus-maze (EPM) and step-down models. Anxiolytic, antidepressant and CNS-depressant studies were evaluated using EPM, Porsolts swim despair and actophotometer models. *Clitoria ternatea* extract (CTE) showed

maximum memory-enhancing and anxiolytic activity ($p<0.001$) at 200 and 100 mg/kg, respectively. Amongst the three plants, *Clitoria ternatea* extract (CTE) showed significant ($p<0.05$) antidepressant activity. All the three plants showed CNS-depressant action at higher dose levels [218].

Treatment with 100 mg/kg of *Clitoria ternatea* aqueous root extract (CTR) for 30 days in neonatal and young adult rats, significantly increased acetylcholine (ACh) content in their hippocampi as compared to age matched controls. Increase in ACh contents in their hippocampus may represent the neurochemical basis for their improved learning and memory [219].

For the studying of the mechanisms of memory enhancement of the Clitoria ternatea aqueous root extract, young adult (60 day old) Wistar rats of either sex were orally intubated with 50 and 100 mg/kg bw of aqueous root extract of *Clitoria ternatea* (CTR) for 30 days, along with age-matched saline controls. These rats were then subjected to passive avoidance tests and the results showed a significant increase in passive avoidance learning and retention. The amygdala of these rats were processed for Golgi staining and the stained neurons were traced using a camera lucida and analysed. The results showed a significant increase in dendritic intersections, branching points and dendritic processes arising from the soma of amygdaloid neurons in CTR treated rats especially in the 100 mg/kg group of rats compared with age-matched saline controls [220].

The effectiveness of alcoholic extracts of aerial and root parts of *Clitoria ternatea* at 300 and 500 mg/kg doses orally was studied in attenuating electroshock-induced amnesia in rats. Extracts at 300 mg/kg dose produced significant memory retention, and the root parts were found to be more effective. In order to delineate the possible mechanism through which *Clitoria ternatea* elicited the anti-amnesic effects, its influence on central cholinergic activity was studied by estimating the acetylcholine content of the whole brain and acetylcholinesterase activity at different regions of the rat brain (cerebral cortex, midbrain, medulla oblongata and cerebellum). The results showed that *Clitoria ternatea* extracts increase rat brain acetylcholine content and acetyl cholinesterase activity, in a similar fashion to the standard cerebro- protective drug, Pyritinol [221].

Neonatal rat pups (7 days old) were intubated with either 50 mg/kg body weight or 100 mg/kg body weight of aqueous root extract of *Clitoria ternatea* (CTR) for 30 days. These rats were then subjected to open field, two compartment passive avoidance and spatial learning (T-Maze) tests (i) immediately after the treatment and (ii) 30 days after the treatment, along with age matched normal and saline control rats. Results showed no change in open field behaviour, but revealed improvement of retention and spatial learning performance at both time points of behavioural tests, indicating the memory enhancing property of CTR which implicates a permanent change in the brain of CTR treated rats [222].

Coriandrum sativum

The effects of fresh *Coriandrum sativum* leaves (CSL) on cognitive functions, total serum cholesterol levels and brain cholinesterase activity was investigated in mice. CSL (5, 10 and 15% w/w of diet) was fed orally with a specially prepared diet, for 45 days consecutively to mice. Elevated plus-maze and passive avoidance apparatus were used as the exteroceptive behavioral models for testing memory. Diazepam, scopolamine and ageing-induced amnesia were used as the interoceptive behavioral models. CSL (5, 10 and 15% w/w of diet) produced a dose-dependent improvement in memory scores of young as well as aged mice. CSL also reversed successfully the memory deficits induced by scopolamine (0.4 mg/kg, ip) and diazepam (1 mg/kg, ip). Brain cholinesterase activity and serum total cholesterol levels were considerably reduced by CSL administration in daily diets for 45 days [223-224].

The effects of inhaled coriander volatile oil (1% and 3%, daily, for 21days) on spatial memory performance were assessed in an Aβ(1-42) rat model of Alzheimer's disease. The Aβ(1-42)-treated rats exhibited the following: decrease of spontaneous alternations percentage within Y-maze task and increase of working memory errors, reference memory errors and time taken to consume all five baits within radial arm maze task. Exposure to coriander volatile oil significantly improved these parameters, suggesting positive effects on spatial memory formation. Assessments of oxidative stress markers in the hippocampal tissue of Aβ(1-42)-treated rats showed a significant increase of superoxide dismutase (SOD), lactate dehydrogenase (LDH) and a decrease of glutathione peroxidase (GPX) specific activities along with an elevation of malondialdehyde (MDA) level. Coriander volatile oil significantly decreased SOD and LDH specific activities, increased GPX specific activity and attenuated the increased MDA level. Also, DNA cleavage patterns were absent in the coriander rats, thus suggesting antiapoptotic activity of the volatile oil. Accordingly, the exposure to coriander volatile oil ameliorated Aβ(1-42)-induced spatial memory impairment by attenuation of the oxidative stress in the rat hippocampus [225].

The effect of *Coriandrum sativum* seed extract on learning was studied in second-generation mice. Ethanolic extract (2%) of coriander was dissolved in sunflower oil as a vehicle and injected (100 mg/kg intraperitoneal) to mother mice during breastfeeding for 25 days at 5-day intervals. After feeding the newborn mice, their learning was evaluated using a step-through passive avoidance task with 0.4 mA electric shock for 2 or 4 seconds. While coriander extract showed a negative effect in the short term (1 hour) after the training

session, it potentiated the mice's learning in later assessments (24 hours post-training [P = 0.022] and 1 week post-training [P = 0.002] by a 4-second shock). Low-dose caffeine (25 mg/kg ip after training) improved the learning after 1 hour (P = 0.024). No modification in the pain threshold was elicited by electric stimuli both in coriander and control groups [226].

Cressa cretica

The effects of *Cressa cretica* was evaluated in learning and memory in mice. Elevated plus maze and passive avoidance paradigm were utilized to test learning and memory. Two doses (200 and 400 mg/kg, po) of ethanolic extract were administered for 28 successive days in separate group of animals. The dose of 400 mg/kg po, of *Cressa cretica* extract (CCE) significantly improved learning and memory of mice. Furthermore, this dose significantly reversed the amnesia induced by scopolamine (0.4 mg/kg, ip). To find out the mechanism by which CCE exerted nootropic activity, the effect of CCE on whole brain AChE activity was also estimated. CCE decreased whole brain acetyl cholinesterase activity and reduced whole brain MDA and NO levels. The antioxidant properties and the presence of flavonoids in *Cressa cretica* may be contributing to memory enhancement effect. Accordigly, *Cressa cretica* was a potent candidate for enhancing learning and memory and it would be beneficial for the treatment of amnesia and Alzheimer's disease [227-229].

Crocus sativus

The recent behavioural and electrophysiological studies have demonstrated that saffron extract affected learning and memory in experimental animals. Saffron extract improved ethanol-induced impairments of learning behaviours in mice, and prevented ethanol-induced inhibition of hippocampal long-term potentiation, a form of activity-dependent synaptic plasticity that may underly learning and memory. Accordingly, saffron extract or its active constituents, crocetin and crocin, could be useful as a treatment for neurodegenerative disorders accompanying memory impairment [230].

Saffron extract was investigated in preventing D-galactose and $NaNO_2$ induced memory impairment and improving learning and memory deficits in amnestic mice. The learning and memory functions in ovariectomized mice were examined by the one way passive and active avoidance tests. In active avoidance test, training in amnestic treated (AT) and amnestic prophylaxis (AP) groups, was improved, there was a significant difference between them and the amnestic control (AC) group. In passive avoidance test, animal's step through latency, as an index for learning, in all test groups was significantly greater than control group. Total time spent in dark room (DS), which opposed the memory retention ability, in AC was significantly greater than AT group at 1 and 2 hours after full training, while there was no significant difference in this parameter between AP and AT [231].

The acute effects of an alcohol extract of *Crocus sativus* (CS-extract) were studied on learning and memory in step through (ST) and step down (SD) tests in normal, trained and memory-impaired mice. A single oral administration of CS-extract had no effects on memory registration, consolidation or retrieval in normal mice. CS-extract reduced the ethanol-induced impairment of memory registration both in ST and SD tests and the ethanol-induced impairment of memory retrieval in SD test. CS-extract decreased the motor activity (MA) and prolonged the sleeping time induced by hexobarbital [116, 232].

Long-term potentiation (LTP) was thought as a generative mechanism underlying learning and memory via storing information in central nervous system. Electro-neurophysiological assay for LTP was generally used in screening the drugs that can facilitate learning and memory. Methanol extract of saffron (MES) being able to facilitate LTP-induction, and can antagonize the inhibiting effect of 30% ethanol on LTP induction (30 pulses/60 Hz) [233].

The effects of *Crocus sativus*, and its active constituent crocin was evaluated on learning and memory loss and the induction of oxidative stress in the hippocampus by chronic stress. Rats were injected with saffron extract, crocin or vehicle over a period of 21 days while being exposed to chronic restraint stress (6 h/day). Then, animals were trained and tested on a water-maze spatial memory task. They performed four trials per day for 5 consecutive days, and this was followed by a probe trial two days later. At the end of the behavioral testing, several parameters of oxidative stress in the hippocampus were measured. Treatment with saffron extractor crocin blocked the ability of chronic stress to impair spatial learning and memory retention. Relative to controls that received vehicle, stressed animals that received saffron extract or crocin had significantly higher levels of lipid peroxidation products, significantly higher activities of antioxidant enzymes including glutathione peroxidase, glutathione reductase and superoxide dismutase and significantly lower total antioxidant reactivity capacity. Crocin significantly decreased plasma levels of corticosterone, as measured after the end of stress. These results indicated that saffron and its active constituent crocin can prevent the impairment of learning and memory as well as the oxidative stress damage to the hippocampus induced by chronic stress[234].

The effect of aqueous extracts of saffron was investigated in morphine-induced memory impairment. On the training trial, the mice were received an electric shock when the animals were entered into the dark compartment. Twenty-four and forty-eight hours later, the time latency for entering the dark compartment was recorded and defined as the retention trial. The mice were divided into (1) control, (2) morphine which received morphine before the training in the passive avoidance test, (3-5) three groups treated by 50, 150 and 450 mg/kg of saffron extract before the training trial, and (6 and 7) the two other groups received 150 and 450 mg/kg of saffron extract before the retention trial. The time latency in morphine-treated group was lower than control ($p<0.01$). Treatment of the animals by 150 and 450 mg/kg of saffron extract before the training trial increased the time latency at 24 and 48 hours after the training trial ($p<0.05$ and $p<0.01$). Administration of both 150 and 450 mg/kg of the extract before retention trials also increased the time latency ($p<0.01$). The results revealed that the saffron extract attenuated morphine-induced memory impairment [235].

Cuminum cyminum

The memory-enhancing and antistress activities of *Cuminum cyminum* were studied in rats. Antistress activity was evaluated by inducing stress via forced swimming and the urinary vanillylmandelic acid (VMA) and ascorbic acid were estimated as biomarkers. Memory-enhancing activity was studied by conditioned avoidance response using Cook's pole climbing apparatus in normal and scopolamine-induced amnestic rats. Daily administration of cumin at doses of 100, 200, and 300 mg/kg bw, 1h prior to induction of stress, it inhibited the stress-induced urinary biochemical changes in a dose-dependent manner without altering the levels in normal control groups. The cognition, as determined by the acquisition, retention, and recovery in rats, was observed to be dose-dependent. The extract also produced significant lipid peroxidation inhibition in comparison with known antioxidant ascorbic acid in both rat liver and brain [236-237].

Cyperus rotuntdus

The effect of the extract and essential oil of *Cyperus rotundus* on memory dysfunction was studied in mice. Cognition was evaluated using the object recognition task that was composed of a square wooden open field box with different shape objects. The test was consisted of three sections: 15 min exploration, first trial for 12 min and second one for 5 min. In the second trial the difference in exploration between a previously seen object and novel one, was considered as an index of memory performance (recognition index). Memory deficit was induced by scopolamine (0.5 mg/kg) before injection of plant extracts and essential oil. Neither the hydroalcholic extracts (100, 200, 400 mg/kg) nor the polyphenolic extract (50, 100, 200 mg/kg) and essential oil (10, 20, 40 mg/kg) of *Cyperus rotundus* produced significant improvement of memory dysfunction [238].

Dalbergia sissoo

The effect of ethanolic leaf extracts of *Dalbergia sissoo* (ELDS) on learning and memory activity was evaluated in mice. ELDS was given as 300, 450 and 600 mg/Kg respectively. The effect of ethanolic leaf extract of *Dalbergia sissoo* was investigated in mice for memory enhancing activity using various experimental paradigms of learning and memory *viz*. Transfer latency (TL) on elevated plus maze and passive avoidance. For memory and learning activity vehicle/ extracts / STD drug administered daily for first seven days, on 8^{th} day dementia was induced by scopolamine. ELDS significantly enhanced the learning and memory activities against the scopolamine induced dementia and significant decrease in Acetylcholinesterase level in brain in animals. The memory enhanced activity as evidenced by learning and retrieval was due to cholinergic facilitatory effect in animals. The results indicated a possible memory enhancing action of *Dalbergia sissoo* which qualitatively comparable with that of piracetam[239].

Daucus carota

The effects of *Daucus carota* seeds on cognitive functions, total serum cholesterol levels and brain cholinesterase activity were studied in mice. The ethanolic extract of Daucus carota seeds (DCE) was administered orally in three doses (100, 200, 400 mg/kg) for seven successive days to different groups of young and aged mice. Elevated plus maze and passive avoidance apparatus served as the exteroceptive behavioral models for testing memory. Diazepam-, scopolamine- and ageing-induced amnesia served as the interoceptive behavioral models. DCE (200, 400 mg/kg, p.o.) showed significant improvement in memory scores of young and aged mice. The extent of memory improvement evoked by DCE was 23% at the dose of 200 mg/kg and 35% at the dose of 400 mg/kg in young mice using elevated plus maze. Significant improvements in memory scores were observed with the using passive avoidance apparatus and aged mice. DCE also reversed the amnesia induced by scopolamine (0.4 mg/kg, ip) and diazepam (1 mg/kg, ip). Daucus carota extract (200, 400 mg/kg, po) reduced significantly the brain acetylcholinesterase activity and cholesterol levels in young and aged mice. The extent of inhibition of brain cholinesterase activity evoked by DCE at the dose of 400 mg/kg was

22% in young and 19% in aged mice. There was a remarkable reduction in total cholesterol level as well, to the extent of 23% in young and 21% in aged animals with this dose of DCE[240].

The effects of *D. carota* seeds was evaluated in memory in rats. The ethanolic extract of *Daucus carota* (DCE) was administered orally in three doses (100, 200 and 400 mg/kg) for seven successive days to different groups of young and aged rats. Elevated plus-maze, Hebb-Williams maze and hexagonal swimming pool were used as exteroceptive behavioral models for testing memory. Diazepam-, scopolamine- and aging-induced amnesia were used as interoceptive behavioral models. DCE (200 and 400 mg/kg, po) induced significant improvement in memory of young and aged rats in elevated plus maze, Hebb Williams maze and hexagonal swimming pool. It also reversed the amnesia induced by scopolamine (0.4 mg/kg, ip) and diazepam (1mg/kg, ip). The results clearly indicated that *D. carota* seeds is a promising therapy to improve memory especially in management of Alzheimer patients[241].

Equisetum arvense

The chronic administration of the hydroalcoholic extract of stems of Equisetum arvense (HAE) reversed the cognitive impairment in aged rats. Chronic administration of HAE at dose of 50 mg/kg, ip, improved both short- and long-term retention of inhibitory avoidance task and ameliorated the cognitive performance in reference and working memory version of the Morris Water Maze. No differences were found between all three groups of young controls, aged controls and EHA-treated animals with regard to the open field and elevated plus maze tests. In vitro assays revealed that HAE diminished the thiobarbituric acid reactive substances as well as nitrite formation, but did not alter catalase activity. The authors concluded that the cognitive enhancement effects of the HAE may be attributed, at least in part, to it antioxidant action[242].

Foeniculum vulgare

The nootropic and anticholinesterase potential of *Foeniculum vulgare* was studied in mice. Methanolic extract of the whole plant of *F. vulgare* administered for eight successive days ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging- induced memory deficits in mice. The passive avoidance paradigm was used as exteroceptive behavioral model for assessing memory. *F. vulgare* extract increased step-down latency and acetylcholinesterase inhibition in mice significantly. The authors postulated that *F. vulgare* can be employed in treatment of cognitive disorders such as dementia and Alzheimer's disease[243].

Glycyrrhiza glabra

The effect of Glycyrrhiza glabra root extract (75, 150 and 300 mg/kg for 2 weeks) was evaluated on learning and memory in three months old male rats. Elevated plus-maze and Morris water maze tests were conducted to evaluate the learning and memory parameters as exteroceptive behavioral model and Diazepam induced amnesia as interoceptive behavioral model. The aqueous extract of root of Glycyrrhiza glabra showed improvement in learning and memory in a dose dependent manner. However, 150 mg/kg dose significantly ($p<0.01$) enhanced learning and memory[244-245].

The beneficial effects of aqueous extract of Glycyrrhiza glabra root extract (75, 150, 225, and 300 mg/kg, for six successive weeks) on learning and memory were studied in 1-month-old male Wistar albino rats using the elevated plus maze, Hebb-William maze, and Morris water maze tests as exteroceptive behavioral model and Diazepam-induced amnesia as interoceptive behavioral model. Results revealed that all the doses of aqueous root extract of Glycyrrhiza glabra significantly enhanced the memory; the doses 150 and 225 mg/kg, possessed significant ($P < 0.01$) enhancement in learning and memory. Furthermore, diazepam-induced amnesia was reversed by the aqueous root extract of Glycyrrhiza glabra (150 and 225 mg/kg, po)[246].

The effects of aqueous extract of Glycyrrhiza glabra (75, 150 and 300 mg/kg po for 7 successive days) on learning and memory was also evaluated in mice. Elevated plus-maze and passive avoidance paradigm were employed to test learning and memory. The dose of 150 mg/kg of the aqueous extract of liquorice significantly improved learning and memory of mice. This dose also significantly reversed the amnesia induced by diazepam (1 mg/kg ip) and scopolamine (0.4 mg/kg ip)[247].

The dose of 150 mg/kg of the aqueous extract of *Glycyrrhiza glabra* for 7 successive days, significantly improved learning and memory of mice and reversed the amnesia induced by diazepam (1 mg/kg p), scopolamine (0.4 mg/kg ip), and ethanol (1 g/kg ip)[248].

The effects of *Glycyrrhiza glabra* on learning and memory were evaluated using object recognition task (ORT) and elevated plus maze (EPM) models in mice. One dose level of aqueous liquorice extract 400mg/kg po and two doses levels of Glabridin rich extract 5mg/kg and 10mg/kg were administered orally in separate groups of animals. aqueous liquorice extract and Glabridin 10mg/kg treatment significantly improved learning and memory of mice by reversing the amnesia induced by scopolamine hydrobromide (2mg/kg, ip) and Diazepam (1mg/kg, ip)[249].

The effect of glabridin isolated from the roots of Glycyrrhiza glabra was investigated on cognitive functions and cholinesterase activity in mice. Glabridin (1, 2 and 4 mg/kg, po) was administered daily for 3 successive days to mice. The higher doses (2 and 4 mg/kg po) of glabridin significantly antagonized the amnesia induced by scopolamine (0.5 mg/kg ip) in both the elevated plus maze test and passive avoidance test. Glabridin (2 and 4 mg/kg po) also remarkably reduced the brain cholinesterase activity in mice compared to the control group[250].

The effect of *Glycyrrhiza glabra* oral supplementation was evaluated on the mental intelligence and memory function of the male students. *Glycyrrhiza glabra* tablets were formulated from the crude powder prepared from roots and subjected to dose standardization process and found suitable without any side effects. 123 students were divided into two group, treatment (1 tablet two times/ day) and placebo control (received starch powder) for the period of 60 days. Each group was further subdivided into two, based on low and high intelligence percentage in order to avoid biasness. Evaluation of improvement was judge by using NVIT (Non Verbal Intelligence Test) and memory test score before the start and at the end of treatment period and scored them accordingly into poor, moderate, good and, very good and expressed in percentage. The overall NVIT results indicated that oral consumption of *Glycyrrhiza glabra* tablets twice a day improved the intelligence level among the student compared to placebo treatment[251].

***Gossypium* species**

The protective effect of *Gossypium herbaceam* extracts (GHE) on learning and memory impairment associated with aging were examined in vivo using Morris water maze and step through task. Furthermore, the antioxidant activity and neuroprotective effect of GHE was investigated histochemically and biochemically. The results showed that oral administration with GHE at the doses of 35, 70, and 140 mg/kg improved the learning and memory impairment in aged rats. It also afforded a beneficial action on eradication of free radicals without influence on the activity of glutathione peroxidase and superoxide dismutase. GHE treatment enhanced the expression levels of nerve growth factor. The proliferation of neural progenitor cells was elevated in hippocampus after the treatment[252].

Hibiscus rosasinensis

The ethyl acetate soluble fraction of the methanol extract of of *Hibiscus rosasinensis* (EASF) attenuated amnesia induced by scopolamine and aging. The discrimination index (DI) was significantly decreased in the aged and scopolamine group in object recognition test (ORT). Pretreatment with EASF significantly increased the DI. In passive avoidance test (PAT), scopolamine-treated mice exhibited significantly shorter step-down latencies (SDL). EASF treatment showed a significant increase in SDL in young, aged as well as in scopolamine-treated animals. The biochemical analysis of brain revealed that scopolamine treatment increased lipid peroxidation and decreased levels of superoxide dismutase (SOD) and glutathione reductase (GSH). Administration of extract significantly reduced LPO and reversed the decrease in brain SOD and GSH levels. The administration of Hibiscus rosasinensis improved memory in amnesic mice and prevented the oxidative stress associated with scopolamine. This effect could be attributed to augmentation of cellular antioxidants[253].

An aqueous extract of *Hibiscus rosa sinensis* showed 62.02%±0.03 (SEM) inhibitory activity against AChE and 57.83%±0.05 (SEM) inhibitory activity against BUChE enzymes respectively. Accordingly, *Hibiscus rosa sinensis* could be useful in improving memory and other cognitive function associated with the cholinergic system[199, 254].

Hibiscus sabdariffa

The nootropic acitivity of calyces of *Hibiscus sabdariffa* was studied in mice using elevated plus maze and passive avoidance paradigm to evaluate learning and memory parameters. The aqueous extracts of calyces of *Hibiscus sabdariffa* (100 and 200 mg/kg, po) significantly attenuated amnestic deficits induced by scopolamine (0.4 mg/kg, ip) and natural aging. *Hibiscus sabdariffa* (100 and 200 mg/kg) decreased the transfer latencies and in-creased step down latencies significantly in the aged mice and scopolamine induced amnesic mice as compared with Piracetam (200 mg/kg, ip). Acetylcholinesterase activity in the whole brain was significantly decreased in mice which could be refere to the underlying mechanism of action[255].

Hypericum triquetrifolium

The crude methanolic extract of the aerial parts of *H. triquetrifolium* was examined for its potential activity in counteracting and preventing cognition impairment caused by acute and chronic restrain stress in rats. *H. triquetrifolium* methanolic extracts were administrated intraperitoneally (50 mg/Kg). Rats were tested for spatial memory in radial arm water maze test. Results revealed that chronic psychosocial stress impairs short term memory. Acute stress also impairs both short term memory and long term memory. Chronic *H.*

triquetrifolium extract administration prevented stress induced memory impairment in both chronic and acute stressed rats which is confirmed by the correction of stress-induced reduction in BDNF protein levels especially in the hippocampal area of brain[256].

Juglans regia

The effects of walnuts on learning and memory was studied in male rats. Walnut was given orally to rats for a period of 28 days. Memory function in rats was assessed by elevated plus maze (EPM) andradial arm maze (RAM). A significant improvement in learning and memory of walnut treated rats compared to controls was observed. Analysis of brain monoamines exhibited enhanced serotonergic levels in rat brain following oral intake of walnuts[257].

The effects of walnut supplementation on motor and cognitive ability were investigated in aged rats. The motor testing showed that the 2% walnut diet improved performance on rod walking, while the 6% walnut diet improved performance on the medium plank walk; the higher dose of the 9% walnut diet did not improve psychomotor performance and on the large plank actually impaired performance. All of the walnut diets improved working memory in the Morris water maze, but the 9% diet showed impaired reference memory[258]. The effects of walnut consumption by mothers during pregnancy and lactation on learning and memory in adult offsprings were studied in rats. The results showed that there was a significant difference in learning and memoryof rat offsprings between experimental and control groups[259].

Juniperus communis

The effects of inhaled juniper volatile oil (1% and 3%, daily, for 21 days) on spatial memory performance were assessed in an Aβ(1-42) rat model of Alzheimer's disease. The Aβ(1-42)-treated rats exhibited decrease of spontaneous alternations percentage within Y-maze task and increase of working memory and reference memory errors within radial arm maze task[260].

VIII. Plants with neuroprotective activity:

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 [261].

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. Treatment with COE significantly attenuated behavioral alterations, oxidative stress, and hippocampal damage in MSG-treated animals [262].

The neuroprotective effect of *Calendula officinalis* flower extract (COE) on 3-NP-induced neurotoxicity in rats was evaluated by observing behavioral changes, OS 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 [263].

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 [264].

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 [265].
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 [266].

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 (*Carthamus tinctorius*), 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[267].

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[268].

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[269].

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[270].

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 ($P<0.05$) [271].

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 [272].

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 [273].

Geriforte, a combination of several plant ingredients (including *Cassia occidentalis*) isbeing used in 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 [274].

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 [275].

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 [276].

Crocus sativus

The protective effect of aqueous saffron extract on neurotoxicity induced by aluminuim chloride ($AlCl_3$) was evaluated in mice. Balb/c and C57BL/6 mice were 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 conclude 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 [277].

The possible reversal effects of saffron against established aluminum (Al)-toxicity was investigated in adult mice. Groups used included Control, 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. Al caused 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[278].

The effect of ethanol extract of *Crocus sativus* was evaluated in 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. 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 CNS and may be potentially useful for the treatment of multiple sclerosis (MS) [279].

The neuroprotective effect of saffron extract, its active component crocin and gamma-glutamylcysteinylglycine (GSH) was studied in glucose-induced neurotoxicity, using PC12 cells as a suitable *in*

vitro model of diabetic neuropathy. Cell viability was quantitated 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 the viability 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 with increased ROS production which reduced by saffron, crocin and GSH pretreatment. The results suggested that saffron and its carotenoid crocin could be potentially useful in diabetic neuropathy treatment [280].

The preventive effect of the aqueous extract of saffron was studied against diazinon (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 [281].

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 [282].

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 [283].

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 endproducts (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. Accordingly saffron extract reduced hyperglycemia and hyperlipidemia risk and also reduced the oxidative stress in diabetic encephalopathy rats [284].

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 [285].

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 [286].

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 [287].

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 [288].

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 humanneuroblastoma SH-SY5Y cells. The results elucidate that pre-treatment of neurons with *Cyperus rotundus* rhizome extract ameliorates 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 extract which 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 [289].

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[290].

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[291].

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 Geum urbanum aqueous extract were 27.03±1.5, 36.48±1.7 and 79.11±3.9 % at concentration of 0.75 mg/ml, 1.5 mg/ml and 3 mg/ml respectiviley and IC_{50} mg/ml was 2.293±0.14, while AChE inhibitory activities of Geum urbanum ethanol extract were 54.74±2.7, 73.53±5.1 and 86.77±5.1 respectively and IC_{50} mg/ml was

0.513±0.03. All the concentration of aqueous and ethanol extracts (0.75 mg/ml, 1.5 mg/ml and 3 mg/ml) inhibited tyrosinase more than 50%, ethanolic extract was more potent tyrosinase inhibitor than aqueous[292].

Hyoscymus niger

The neuroprotective potential, of petroleum ether and aqueous methanol extracts of *Hyoscyamus niger* seeds was evaluated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson disease in 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[293].

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, rotarod 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[294].

Juglans regia

The neuro-protective 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[295].

The neuro protective 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 in MPTP 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[296].

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[297].

Conclusion

The review discussed the medicinal plants affected the central nervous system as sedative, anticonvulsant, antidepressant, antipsychotic, anxiolytic, anti-Parkinson, memory-enhancing, locomotor and neuroprotective, as promising source of drugs because of their safety and effectiveness.

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