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Medicinal plants with central nervous effects (part 2): plant based review

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Abstract: Previous reviews revealed that many medicinal plants affected central nervous functions and can be utilize for therapeutic purposes as antiepileptic, antidepressant, anxiolytic, sedative, anti-Parkinson, antipsychotic, neuroprotective and many other effects. This review will highlight the central nervous effects of medicinal plants as a second part of our previous review.

Keywords*: medicinal plants, herbs, CNS, antiepileptic, antidepressant, anxiolytic, sedative, anti-Parkinson, antipsychotic, neuroprotective*

I. INTRODUCTION

Plants are a valuable source of a wide range of secondary metabolites, which are used for treatment and prevention of the diseases. A lot of plant active ingredients were isolated and characterized, and their pharmacological effects and mechanisms of action were understood. Previous reviews showed that medicinal plants possessed wide range of central nervous effects [1-4]. These plants included: *Alhagi maurorum* [5], *Anchusa italic* [6], *Anthemis nobelis* [7], *Antirrhinum majus* [8], *Apium graveolens* [9], *Arachis hypogaea* [10], *Arctium lappa* [11], *Arundo donax* [12], *Asparagus officinalis* [13], *Avena sativa* [14], *Bacopa monniera* [15], *Ballota nigra* [16], *Bellis perennis* [17], *Benincasa hispida* [18], *Brassica nigra* [19], *Bryophyllum calycinum* [20], *Caesalpinia crista* [21], *Calendula officinalis* [22], *Calotropis procera* [23], *Capsella bursa-pastoris* [24], *Carum carvi* [25], *Carthamus tinctorius* [26], *Cassia occidentalis* [27] and *Centaurea cyanus* [28]. This review was designed to cover the plant with antiepileptic, antidepressant, anxiolytic, sedative, anti-Parkinson, antipsychotic, neuroprotective and other central nervous pharmacological and therapeutic effects.

II. PLANTS WITH CENTRAL NERVOUS EFFECT

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 [29-31].

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 [32].

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 [33].

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 [34].

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 [35-36].

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 [37].

Citrus species

Preliminary behavioral screening performed with the lemon fruit demonstrates that it promoted sleep in dementia increasing motivational behaviour and improving disturbed behavior [38-39].

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 [40].

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 [41].

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 [42].
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 [43].

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 [44].

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 [45].

Factors that enhance the intrinsic growth potential of neurons play a major role in the regeneration and repair of adult neurons following an injury. Fibroblast growth factor (FGF-2) is one of the key players in the origin and growth of neuronal and glialcells through autocrine and paracrine signaling. Water extract of *Citrus medica* var. sarcodactylis, was found to activate the FGF-2 promoter in transgenic luciferase expression models. *Citrus medica* treatment on Schwann cells (RSC96) transfected with luciferase reporter plasmid under a FGF-2 promoter, was found to induce the FGF-2 promoter and showed enhanced luciferase expression. The FGF-2 expression was accompanied with an increase in the expression of proteins involved in cell migration and cell proliferation in a dose dependent manner [46].

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 [47].

Clerodendrum inerme

Tics are characterized by involuntary, sudden, rapid, repetitive, non-rhythmic, stereotyped movements or phonic productions. A report of a 13-year-old girl, with chronic motor tic disorder refractory to multiple anti-tic therapies, showed dramatic improvement and remission after taking the crude leaf extract of *Clerodendrum inerme* (L) Gaertn. No side effects were observed during a follow-up of more than 2 years [48-49].

The effect of the ethanol extract of *Clerodendrum inerme* leaves was evaluated in animal behaviors mimicking Tourette syndrome (TS), hyper-locomotion, and sensori-motor gating deficit. The latter is also observed in schizophrenic patients and can be reflected by a disruption of prepulse inhibition of acoustic startle response (PPI) in animal models induced by methamphetamine and NMDA channel blockers (ketamine or MK-801), based on hyperdopaminergic and hypoglutamatergic hypotheses, respectively. *Clerodendrum inerme* extract (10–300 mg/kg, ip) dose-dependently inhibited hyperlocomotion induced by methamphetamine (2 mg/kg, ip) and PPI disruptions induced by methamphetamine, ketamine (30mg/kg, ip), and MK-801 (0.3 mg/kg, ip) but did not affect spontaneous locomotor activity, rotarod performance, and grip force. Accordingly,

Clerodendrum inerme extract can relieve hyperlocomotion and improve sensorimotor gating deficit, supporting the therapeutic potential of *Clerodendrum inerme* for TS and schizophrenia [50].

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 [50-51].

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 [52].

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 [53].

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 [54].

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 [55].

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 [56].

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 [57].

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 [58].

The effect of aqueous and hydroalcoholic extracts of *Clitoria ternatea* on biochemical and behavioral parameters related to cognitive impairment was studied *in vitro* and *in vivo*. *In vitro* free radical scavenging and enzyme-inhibitory (cholinesterase, glycogen synthase kinase-3-β, rho kinase, prolyl endopeptidase, catechol-O-methyl transferase, and lipoxygenase) activities of aqueous and hydroalcoholic extracts of *Clitoria ternatea* plant were evaluated. Based on *in vitro* results, hydroalcoholic extract of *Clitoria ternatea* (100, 300, and 500 mg/kg, po) was selected for evaluation in intracerebroventricularly injected streptozotocin (STZ)-induced cognitive impairment in male Wistar rats. Behavioral assessment was performed at baseline and on the 14th, 21st, and 28th days after STZ injection using elevated plus maze, passive avoidance, Morris water maze, and photoactometer. Oxidative stress parameters (malondialdehyde, reduced glutathione, nitric oxide levels, and superoxide dismutase activity), cholinesterase activity, and rho kinase (ROCK II) expression were studied in cerebral cortex and hippocampus of rats' brain at the end of the study. The hydroalcoholic extract possessed significantly more *in vitro* antioxidant and enzyme-inhibitory activities as compared to aqueous extract. The hydroalcoholic extract of *Clitoria ternatea* prevented STZ-induced cognitive impairment dose dependently, by reducing oxidative stress, cholinesterase activity, and ROCK II expression. The authors concluded that *in vitro* and *in vivo* results suggest the potential of hydroalcoholic extract of *Clitoria ternatea* for treatment of cognitive deficit in neurological disorders [59].

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 [60].

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% [61-62].

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 [61-63].

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 [64-65].

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 [66].

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 [67].

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 [68-69].

The effect of the hydroalcoholic extract of *Coriandrum sativum* leaves on the exploratory behaviour pattern and locomotor activity was investigated in mice. Elevated plus maze (EPM) and open field test (OFT) were used to assess the anxiolytic activity of the extracts. Diazepam (1 mg/kg) was used as standard anxiolytic agent. The 200 and 400 mg / kg body weight of the crude dried extract and diazepam produced highly significant (P<0.01) anxiolytic effects, in a dose-dependent manner, by increasing the time spent on, and the number of entries into the open arms of the EPM and by an increase in the locomotion by mice in the OFT. However, in lower doses the extract did not affect the locomotor activity [70].

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 [71-72].

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 [73].

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 [74].

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 [75].

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 [76].

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 [77].

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 [78].

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 [79].

The effect of ethanolic extract of *Coriandrum sativum* seeds (100, 200 mg/kg) was studied on tacrine induced orofacial dyskinesia. Tacrine (2.5 mg/kg, ip) treated animals were observed for vacuous chewing movements (VCM), tongue protrusions (TP) and orofacial bursts (OB) for 1 h followed by observations for locomotor changes and cognitive dysfunction. Subchronic administration of *Coriandrum sativum* seed extract (E-CS) (100, 200 mg/kg, po, for 15 days significantly ($P<0.05$) decreased the tacrine induced VCM, TP and OB; and also significantly ($P<0.05$), increased locomotion and cognition compared to the tacrine treated group. Biochemical analysis revealed that tacrine administration significantly ($P<0.05$) decreased the levels of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSH) levels and also significantly ($P<0.05$) increased lipid peroxidation (LPO) as an index of oxidative stress, whereas subchronic administration of E-CS significantly ($P<0.05$) improved the antioxidant enzyme (SOD, CAT, and GSH) levels and also significantly ($P<0.05$) decreased lipid peroxidation (LPO). The results have demonstrated the protective role of ethanolic extract of *Coriandrum sativum* against tacrine induced orofacial dyskinesia [80].

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 [81].

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 [82].

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 [83-85].

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 [86-87].

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 [88].

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 [89].

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 [90].

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 [88, 91-93].

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 1st and 21st. 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 [94].

The anticonvulsant activity of the aqueous (0.08-0.8 g/kg) and ethanolic extracts (20-40 mg/kg) of *Crocus sativus* stigma (CSS) was studied in mice using pentylenetetrazole (PTZ) and the maximal electroshock seizure (MES) tests. In the PTZ test, CSS delayed the onset of tonic convulsions, but failed to produce complete protection against mortality. In the MES test, both extracts decreased the duration of tonic seizures [95].

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 [96].

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 [97].

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 [98].

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 [99].

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 [100].

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[101].

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 [102].

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 [103].

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 [104].

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 [105].

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 [99].

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) [106].

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 [107].

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 [108].

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 [109].

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 [110].

The protective and therapeutic effects of aqueous and ethanolic extracts of *Crocus sativus*, and its active consistent, safranal, was studied in the harmaline-induced tremor in mice. To induce tremor, harmaline (30 mg/kg) was injected intraperitoneally. Test groups were also given the aqueous and ethanolic extracts of saffron (40, 80, and 160 mg/kg) or safranal (0.1, 0.3, and 0.5 ml/kg), intraperitoneally, 10 min before harmaline administration (prophylactic study) or 10 min after the onset of tremors (curative study). The latency of onset, duration, and intensity of tremor were recorded. The extracts (80 and160 mg/kg) dose dependently attenuated duration of harmaline-induced tremors as did reference drug (propranolol 2 and 5 mg/kg). Only the highest dose of extracts (160 mg/kg) attenuated intensity of harmaline-induced tremors. Safranal at the doses of (0.1 and 0.3 ml/kg) but not 0.5 ml/kg attenuated duration and intensity of tremor. Onset of tremor increased with the extracts (80 and 160 mg/kg) in prophylactic study, as the effect observed with propranolol at the dose of 5 mg/kg. Safranal did not affect the latency of tremor [111].

The effects of aqueous and ethanolic extracts of *Crocus sativus* stigma and its constituents were evaluated on morphine-withdrawal syndrome in mice. Dependence was induced using subcutaneous injections of morphine for 3 days. On day 4, morphine was injected 0.5 h prior the interaperitoneal injections of the extracts, crocin, safranal, clonidine (0.3 mg/kg) or normal saline. Naloxone was injected (5 mg/kg ip) 2 h after the final dose of morphine and the number of episodes of jumping during 30 mm was considered as the intensity of the withdrawal syndrome. Clonidine, the aqueous and ethanolic extracts of saffron reduced the jumping activity. Safranal injected (sc) 30 mm prior and 1 and 2 h after the injection of morphine potentiated some signs of withdrawal syndrome. The aqueous extract decreased the movement in all doses (80, 160, 320 mg/kg) and the ethanolic extract decreased it in the dose of 800 mg/kg in open field test. But crocin and the dose of 400 mg/kg ethanolic extract showed no effect on activity in this test. The authors concluded that the extracts and crocin may interacted with the opioid system to reduce withdrawal syndrome [112].

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 ($p\leq0.001$) 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 ($p\leq0.001$) 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 [113].

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[114].

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) [115].

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 [116].

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 [117].

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 [118].

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 [119].

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 [120].

The effects of saffron ethanolic extract and its constituent, safranal, on the acquisition and expression of morphine-induced place preference (CPP) were investigated in male Swiss Webster mice. An unbiased place conditioning method was applied for assessment of morphine reward properties. The saffron extract and safranal were administered intraperitoneally during (acquisition) or after induction (expression) of morphine CPP. In a pilot study, the extract and safranal were alone administered to the animals to assess if they have any reward properties. Subcutaneous of morphine (4 and 8 mg/ kg) and extract (50 mg/ kg; ip) induced CPP. Extract (10, 50 and 100 mg/ kg; ip) reduced the acquisition and expression of morphine- induced place preference. The same results were obtained when safranal (1, 5 and 10 mg/ kg, ip) was used [121].

The effect of hydroethanolic saffron extract (CSE) and trans-crocetin was investigated on synaptic transmission. Postsynaptic potentials (PSPs) were elicited by focal electrical stimulation and recorded using intracellular placed microelectrodes in pyramidal cells from rat cingulate cortex. CSE (10-200 μg/ml) inhibited evoked PSPs as well as the isolated NMDA and non-NMDA component of PSPs. Glutamate (500 μM) added into the organ bath induced membrane depolarization. CSE decreased glutamate-induced membrane depolarization. Additionally, CSE at 100 μg/ml decreased NMDA (20 μM) and kainate (1 μM)-induced depolarization, whereas AMPA (1 μM)-induced depolarization was not affected. Trans-crocetin (1-50 μM) showed inhibition of evoked PSPs and glutamate-induced membrane depolarization comparable to CSE. Trans-crocetin at 10 μM decreased NMDA (20 μM)-induced membrane depolarization, but did not inhibit the isolated non-NMDA component of PSPs. The authors conclude that trans-crocetin was involved in the antagonistic effect of CSE on NMDA but not on kainate receptors [122].

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 [123].

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 [124-125].

The effects of fruit essential oil (FEO) of *Cuminum cyminum* on acquisition and expression of morphine tolerance and dependence were investigated in mice. Animals were rendered dependent on morphine

using the established method in which morphine (50, 50, 75 mg/kg; sc) was injected three times daily for 3 days. FEO (0.001, 0.01, 0.1, 0.5, 1 and 2%; 5 ml/kg, ip) or Tween-80 (5 ml/kg, ip) were given 60 min prior to each morphine injection (for acquisition) or the last injection of morphine on test day (for expression). Morphine tolerance was measured by tail-flick before and after administration of a single dose of morphine (50 mg/kg, sc) in test day (4^{th} day). Morphine dependence was also evaluated by counting the number of jumps after injection of naloxone (5 mg/kg, ip) on the test day. The results showed that Cumin FEO, only at the dose of 2%, significantly attenuated the development of morphine tolerance ($p<0.01$) and dependence ($p<0.05$). It was significantly effective on expression of morphine tolerance (1 and 2%) and dependence (0.5, 1 and 2%) in a dose-dependent manner. Accordingly, the essential oil of *Cuminum cyminum* ameliorated the morphine tolerance and dependence in mice[126].

The effects of *Cuminum cyminum* fruit essential oil (FEO) on the acquisition and expression of morphine-induced conditioned place preference (CPP) was studied in mice. CPP was induced by subcutaneous injection of morphine (5mg/kg) in 3 days conditioning schedule. Intraperitoneal administration of Cumin FEO (0.001%, 0.01%, 0.1%, 0.5%, 1% and 2%; 5 ml/kg) or Tween-80 (0.5%, 5 ml/kg) did not show any conditioning effects. Administration of Cumin FEO (0.001-2%, 5 ml/kg; ip), 60 min before test on day 5 (expression) decreased the conditioning scores at the doses of 1% and 2% while ip injection of Cumin FEO (0.001-2%, 5 ml/kg), 60 min before morphine injection (5mg/kg, sc) during 3 days of conditioning session (acquisition) significantly resulted in decrement of rewarding properties of morphine at the doses of 0.1%, 0.5%, 1% and 2% in dose-dependent manner [127].

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 [128].

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 [129].

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 [130-131].

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[132].

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[133].

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[134].

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 [135].

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 [136-137].

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 [128].

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[139].

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 [138].

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 [140].

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 [141-142].

Open field, head dip, rearing traction and forced swimming test were used to study the neuropharmacological of 300 and 500mg/kg of *Cyperus rotundus* extract. The crude extract showed mild decreased in all tests and exhibited slight muscle relaxant effect [143].

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 [144].

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 [145].

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 [146].

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 [147].

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 ($p \leq 0.05$) 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 [148].

Pretreatment with the ethanol extract of *Cyperus rotundus* caused significant protection against strychnine and leptazol-induced convulsions [144].

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 [149].

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 [150].

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 [151].

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 [152].

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 [153].

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 [154].

III. CONCLUSION

This review covered the central nervous effects of the medicinal plants, including plants with hypnotic, anticonvulsant, antidepressant, antiparkinson, antipsychotic, anxiolytic, anti-fatigue, memory-enhancing and skeletal muscle relaxant effects .

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