THERAPEUTIC PROPERTIES OF MEDICINAL PLANTS: A REVIEW OF MEDICINAL PLANTS WITH CENTRAL NERVOUS EFFECTS (PART 1)

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ABSTRACT

The recent studies showed that many plants affected the central nervous system and exerted many pharmacological effects including hypnotic, anticonvulsant, antidepressant, anti-Parkinson, antipsychotic, anxiolytic, anti-fatigue, memory-enhancing, skeletal muscle relaxant effect, decreasing of morphine and nicotine withdrawal and other effects. This review will highlight the central nervous effects of the medicinal plants.

Keywords: Medicinal plants, CNS, Hypnotic, Anticonvulsant, Antidepressant, Antiparkinson, Antipsychotic, Anxiolytic, Memory-enhancing, Skeletal muscle relaxation.

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. The recent studies showed that many plants affected the central nervous system and exerted many pharmacological effects. They were beneficial in many neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, dementia, stress and fatigue, brain trauma, depression, epilepsy, anxiety, psychosis, cognitive dysfunction, mental dysfunction, learning and memory disorders, and ischemia of the central nervous systems [1-49]. This review will highlight the central nervous effects of the medicinal plants

*Alhagi maurorum*

*Alhagi maurorum* decreased the locomotion activity of the animals and skeletal muscle relaxation. Exposure of the frog’s rectus abdominis muscle to the extract in a concentration of 4 μg/ml bathing fluid for 5 min antagonized ACh (3 μg/ml)-induced contraction by 70 ± 2.1% (N = 4). When the dose of ACh was increased up to 8 μg/ml in the presence of the extract blockade, it did not reverse completely the blockade. The maximum reversal of antagonism was 27.7, suggesting that the extract blocked the action of ACh in a non-competitive manner. Intraperitoneal administration of the ethanolic extract (EE) of *Alhagi maurorum* powdered roots into conscious mice in doses of 1.6 g/kg produced mild sedation. The extract also decreased the locomotion activity of the animals and skeletal muscle relaxation suggesting an action at the skeletal muscles neuromuscular junctions [50].

*Anchusa italica*

Oral administration of Abnormal Savda Munsiq (ASMq) which contained *Anchusa italica*, also found to exert a memory-enhancing effect in the chronic stressed mice induced by electric foot-shock. The memory improvement of the stressed mice was shown by an increase of the latency time in the step-through test and the decrease of the latency time in the Y-maze test. Treatment with ASMq induced significant decrease in the serum levels of adrenocorticotropic hormone.

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corticosterone and β-endorphin as well as the brain and serum level of norepinephrine. Furthermore, ASMq was able to significantly reverse the chronic stress by decreasing the brain and serum levels of the monoamine neurotransmitters dopamine, 5-hydroxytryptamine and 3, 4-dihydroxyphenylalanine [51].

**Anthemis nobelis**

In mice, apigenin had a clear affinity for central benzodiazepine receptors. Apigenin competitively inhibited the binding of flunitrazepam, a benzodiazepine, but had no effect on muscarinic receptors, alpha 1-adrenoceptors, or the binding of muscimol to GABA receptors. Apigenin had clear anxiolytic activity in mice without incidence of sedation or muscle relaxation effects at doses similar to those used for classical benzodiazepines; no anticonvulsant action was detected. Increasing dosages produced mild sedation and a reduction in ambulatory locomotor activity [52-53].

**Antirrhinum majus**

Aurones belong to the family of flavonoids, structurally isomers of flavones, were synthesised in Antirrhinum majus [54-55]. They were named as benzylidenebenzofuran-3(2H)-ones. Aurones and extracts comprising them were useful in the prophylactic and/or therapeutic treatment of an animal (including a human) with a phosphodiesterase (PDE) dependent disease or condition of the central nervous system. Among the diseases and conditions of the nervous system to be treated prophylactically or therapeutically, neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, age related dementia or dementia in general, neurological trauma including brain or central nervous system trauma, depression, anxiety, psychosis, cognitive dysfunction, mental dysfunction, learning and memory disorders, and ischemia of the central and/or peripheral nervous systems [56].

**Apium graveolens**

The anti-depressant effect of methanic extract of Apium graveolens seeds (AGM) was investigated using two behavioral models in in-vivo study, the AGM (100, 200 mg/kg) produced significant anti-depressant effect on mice and rats in both forced swim test and tail suspension test, its action was found to be similar to imipramine. The anti-depressant effects of AGM were more prominent at 200 mg/kg when compared to lower dose of same fraction. The 3, n-butylphthalide and sedanenolide isolated from celery oil showed weak sedative activity, prolonged pentobarbital narcosis, and induced sleep immediately following recovery from a prior barbiturate treatment in mice [57].

**Arachis hypogaea**

Cho-K1 cells stably transfected with opioid receptor subtypes μ, Δ, and κ was used to assay the affinity of peanut constituents to opioid receptors. Compound GC-143-8 was run in competition binding against all three opioid subtypes (μ, κ, and Δ). One of peanut stilbenoids showed opioid receptor affinity. Combined use of this compound and analgesic agents may result in lower amounts of the latter needed to block pain. However, it is likely that the specific position and number of hydroxy groups in the structure of the stilbenoid may be responsible for opioid receptor binding [59].

Arachis hypogaea leaf aqueous extracts have received a long reputation as an abirritative remedy to ease various sleep disorders. The clinical studies confirmed the hypnotic effects of Arachis hypogaea [60-61]. The sedative effects of Arachis hypogaea leaf aqueous extracts on brain ATP, AMP, adenosine and glutamate/GABA of rats was investigated. Intragastrically administrated Arachis hypogaea leaf aqueous extracts (PLAE, 100 and 500 mg/kg body weight BW) and peanut stem aqueous extracts (PSAE, 500 mg/kg BW) for at least 14 days, showed that brain lactate were significantly elevated (p < 0.05) in rat cerebrums after PLAE administrations, compared with control and PSAE groups. A significant degradation of the brain adenosine triphosphate (ATP) (p < 0.05) was observed in the brain-stems and even the whole brains of rats of PLAE treatments. Moreover, the brain adenosine monophosphate (AMP) were clearly decreased (p < 0.05) in rat cerebrum and brainstem regions, while the brain adenosine revealed an increasing propensity (p = 0.076) in the cerebrums of freely behaving rats. The γ-aminobutyric acid (GABA) concentrations were statistically (p < 0.05) enhanced and the ratios of Glutamate/GABA were simultaneously reduced (p < 0.05) in rat brainstems, no matter which dose (100 or 500 mg/kg BW) of PLAE were used [62].

**Arctium lappa**

The anti-fatigue effect of the extract of Arctium lappa L. was studied in male mice by forced swimming test. The swimming time of mice treated by 4 and 6 g/kg of an extract of Arctium lappa was significantly prolonged as compared with control group. The hepatic glycogen storage in the groups treated with 2, 4 and 6 g/kg of Arctium lappa extract was significantly increased. Lactic acid clearance in the groups treated with 4, and 6 g/kg of Arctium lappa extract was significantly accelerated after mice swimming [63].

**Arundo donax**

The rhizome of Arundo donax contained at least five tryptamines, including N,N-DMT, 5-MeO-DMT and bufotenine. It was reported that it produced no psychoactive effects, 50 mg of rhizome extract did not produce psychedelic effects, but instead, it caused mild but long lasting allergic reactions, which include blurred vision, watery and swollen eyes, conjunctivitis, and hives.
Avenasativa

Avenasativa exerted antifatigue effects, enhanced anoxia tolerance, induced analgesia and improved memory, as well as decreased the contents of lipid peroxide in plasma, liver and brain of the animal [67].

Asparagus officinalis

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Avena sativa

An extract of wild green oat (Avenasativa L.), was tested in vivo in rats for its behavioural effects after chronic oral administration via extract-admixed food. Rats received 10 g/kg and 100 g/kg extract-admixed food showed slight decreased food and fluid intake in the high dose group, with no side effects observed during the treatment. The low dose led to an improvement of active stress response, an enhancement of shock avoidance learning and an increased synchrony in social behavior [68].

Dietary oat β-glucan enhanced the endurance capacity of rats and facilitated their recovery from stress and fatigue. Sparsgue-Dawley rats, fed with/without oat β-glucan 312.5 mg/kg/day for 7 weeks, were subjected to run on a treadmill system to make them exhausted. All rats were immediately sacrificed after prolonged exercise, and the major metabolic substrates were measured in serum and liver. The results showed feeding dietary oat β-glucan to rats significantly reduce the body weight and increase the maximum running time compared with normal control (P<0.05). Furthermore, dietary oat β-glucan decreased the levels of blood urea nitrogen, lactate acid, and creatine kinase activity in serum, and increased the levels of non-esterified fatty acids, lactic dehydrogenase activity in serum, and the content of liver glycogen [69].

Avenasativa improved overall mental fitness and supported cognitive performance in stressful situations. Avenasativa has been shown to positively affect the activity of brain enzymes closely related to mental health and cognitive function in-vitro. Additionally, preclinical and clinical studies have confirmed that Avena sativa specifically interacted with brain structures and neurotransmitters implicated in cognition, memory and motivation. Avena sativa boasted a dual activity profile on monoamino oxidase-B (MAO-B) and phosphodiesterase 4 (PDE4) thus displayed in its ability to mediate a strengthening and balancing effect on the brain and mind [70].

The dried seeds and fresh plant exerted antidepressant activity, and it was useful where lowered mood is associated with anxiety and nervous exhaustion, especially during menopause. The fresh plant is a tonic remedy for all types of nervous debility, and can help to improve sleep duration and quality where the person is literally too tired to sleep. Oats also aid withdrawal from tobacco and drug addiction [71]. A dose of 1600 mg of oat herb extract acutely improve attention and concentration and the ability to maintain task focus in older adults with differing levels of cognitive status [72]. However, the aqueous extract prepared from the tincture did not affect the seizure threshold to bemepride or nicotine or the sleeping time induced by barbitone sodium [73].

The biological effects of Avenasativa has been investigated in laboratory animals following a report that tincture of Avenasativa reduced the craving for cigarettes in man. When the tincture evaporated to dryness, reconstituted in an equal volume of water and administered by stomach tube or intraperitoneal injection, it antagonized the antinociceptive effect of morphine in two separate test (hot-plate and tail flick). Compared with animals made dependent on morphine, mice pretreated with repeated injections of morphine plus extract passed a smaller number of stools and tended to jump less after administration of nalorphine [74].

An alcoholic extract of green oats was tried on opium addicts. Six chronic opium addicts gave up opium completely, two reduced their intake and two showed no change following regular use of 2 ml three times daily (human clinical study). A significant diminishment of the number of cigarettes used by habitual tobacco smokers resulted from using 1 ml (four times daily) of fresh Avena sativa alcoholic extract of mature plants [75].

The pressor response to intravenously administered nicotine in urethane-anaesthetized rats was also antagonized by prior administration of Avena sativa [73]. An alcoholic extract of common oats (Avena sativa) has been reported to reduce both the craving for, and the number of, cigarettes smoked per day [76]. Hundred non-hospitalized smokers with an average consumption of 20 cigarettes per day were treated with an alcoholic extract of Avena sativa for disaccustoming. There was difference of disaccustoming between light and heavy smokers. The rate of disaccustoming was higher for light smokers than for smokers with a high consumption of cigarettes [77].

Bacopa monniera

Behavioral studies in animals have shown that Bacopa improves motor learning, acquisition and retention, and delay extinction of newly acquired behavior [78]. The methanol extract and different fractions of Bacopa monniera were evaluated for antidepressant activity in the forced swimming test (FST) and tail suspension test (TST) in mice. The results showed that the methanol extract, ethanol and butanol fraction significantly reduced the immobility times both in FST and TST in mice after being administrated orally for 5 consecutive days. All tested samples, in the effective doses for FST and TST, showed no inhibitory effect against locomotor activity (LA) in mice [79]. On the other hand, it was found that...
bacosides facilitates anterograde memory and attenuate anterograde experimental amnesia induced by scopolamine and sodium nitrite possibly by improving the acetylcholine level and hypoxic conditions, respectively. In addition, bacosides also reversed BNS2021 (a platelet-activating factor receptor antagonist) induced retrograde amnesia, probably due to increase in platelet activating factor synthesis by enhancing cerebral glutamate level [80]. Memory deficits following cholinergic blockade by scopolamine were reversed by Bacopa treatment. Bacopa improved memory functioning in cognitively intact cohorts, with Pycnogenol improving working memory[81]. Benzodiazepines are known to produce amnesia by the involvement of GABAergic system and by the interference of long term potentiation. The behavioral study showed that Bacopa monniera significantly reversed the diazepam induced amnesia [82]. Bacopa administration with phenytoin significantly reversed phenytoin-induced cognitive impairment, as noted by improved acquisition and retention of memory [83]. A clinical trial was carried out to assess the effects of 12-weeks administration of Bacopa monnieri (300mg/day) on memory performance in people over the age of 55-years. Bacopa significantly improved memory acquisition and retention in older persons [84]. Significant cognitive enhancing benefits have been demonstrated with chronic administration of Bacopa extracts. A double-blind, placebo-controlled, 12-week trial utilizing the same patient selection criteria and the same dose of Bacopa extract (300 mg daily) containing 55% combined bacosides, was carried out. Forty-six healthy volunteers (ages 18-60) were randomly and evenly divided into treatment and placebo groups. The same series of tests administered in the acute dosage trial were administered at baseline, five, and 12 weeks after treatment began. At the end of the 12-week study, results indicated a significant improvement in verbal learning, memory consolidation, and speed of early information processing in the treatment group compared to placebo. These effects were not observed at baseline or at five weeks[85].

The Bacopa supplement was commercially available as KeenMind™ (Flordis). This product is manufactured from the stems, leaves and roots of Bacopa and is extracted with 50% ethanol. It is standardized to contain active bacosides at levels of 55% ± 5%. KeenMind™ help develop novel preventative health practices and nutritional/pharmacological targets in the elderly for cognitive and brain health. Bacopa appeared to have multiple modes of action in the brain, all of which may be useful in ameliorating cognitive decline in the elderly. These include: (i) direct pro-cholinergic action; (ii) anti-oxidant (flavonoid) activity; (iii) metal chelation; (iv) anti-inflammatory effects; (v) improved blood circulation; (vi) adaptogenic activity; and (vii) removal of b-amyloid deposits[86]. However, in a double-blind randomized, placebo control study performed on 76 adults aged between 40 and 65 years, in which various memory functions were tested and levels of anxiety was measured, the rate of learning was unaffected by Bacopa monnieri suggesting that Bacopa monnieri decreases the rate of forgetting of newly acquired information. Tasks assessing attention, verbal and visual short-term memory and the retrieval of pre-experimental knowledge were unaffected. Questionnaire measures of everyday memory function and anxiety levels were also unaffected [87].

Bacopasides A and B, bacopasides I and II and bacopasaponin C and the extract of Bacopa monniera exhibited antidepressant activity, while bacopaside VII did not have any antidepressant activity when tested on forced swimming and tail-suspension models in experimental animals[88-90].

Crude plant extract of Bacopa monnieri or bacosides have also shown anxiolytic effects, antidepressant activity, anticonvulsant action and antioxidant activity[91]. Bacopa monnieri was highly effective as an adaptogen, it normalized acute and chronic stress induced corticosterone changes in rats. It also normalized noradrenalin (NA), 5-HT, and DA in cortex and hippocampus of rats in acute and chronic unpredictable stress[92]. Bacopa modulated the cholinergic system and have antioxidant and metal chelating effects. In an animal model, there was a dose-related reversal by Bacopa of cognitive deficits produced by the neurotoxins, colchicine and ibotenic acid [93-94]. Bacopa monnieri lowered norepinephrine and increases the 5-hydroxytryptamine levels in hippocampus, hypothalamus and cerebral cortex. The higher doses of Bacopa monniera extracts produced significantly greater anxiolytic effects compared to lorazepam, a standard anxiolytic drug from benzodiazepine group [95]. However, acute and sub chronic (one week) treatment of Bacopa monnieri methanolic extract (10, 20 or 30 mg/kg) didn’t affected dopamine (DA) and serotonin (5-HT) turnover in mice whole brain[96].

Bacopa monnieri, on pharmacological Caenorhabditis elegans models of Parkinson’s, reduced alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent[97].

Crude plant extract of Bacopa monnieri or bacosides have also shown anticonvulsive action. It possessed neuroprotective effects in glutamate-mediated excitotoxicity during seizures and cognitive damage occurring inassociation with pilocarpine-induced epilepsy[98]. The ethanolic extract of Bacopa monniera was tested for anticonvulsant activity using different convulsive models (pentyleneetrazol, maximal electroshock and strychnine-induced convulsion in rats, as well as hypoxic stress-induced convulsions in mice and lithium–pilocarpine-induced status epilepticus). The ethanolic extract of Bacopa monniera was administered as
50 and 55 mg/kg orally for rats and mice, respectively, 2 and 4 hours before the respective convulsive stimuli. The ethanolic extract of leaves produced significant anticonvulsant activity for all the different models studied with a mechanism of action similar to that of benzodiazepines (GABA agonist)[99].

**Ballota nigra**
Phenylpropanoid derivatives isolated from *Ballota nigra* showed neurosedative activity and exhibit potent antioxidant activities which are of therapeutic interest [100-101]. The ability of five phenylpropanoids (verbascoside, forsythoside B, arenarioside, ballotetoside, and caffeoyl malic acid) isolated from a hydroalcoholic extract, to bind to benzodiazepine, dopaminergic, and morphinic receptors was investigated. To carry out these studies, affinity tests with rat striata, entire brains and receptor rich preparations were employed. Results show that four of the five compounds are able to bind to the studied receptors. Inhibitory concentrations at 50% were determined and vary from 0.4 to 4.7 mg/ml. This may be in relation with the *Ballota nigra* known neurosedative activities [102].

**Bellis perennis**
The effects of aqueous extract of flowers from *Bellis perennis* on anxiety-like behavior and memory in Wistar rats were tested. *Bellis perennis* (20 and 60 mg/kg) administrated rats, spent more time at the center, showed less mobility and velocity. In the elevated plus maze, the high dose of *Bellis perennis* administrated rats spent more time in the open arms, spent less time in the closed arms, were less mobile, were slower and rotated less frequently. In the Morris water maze, the high dose of *Bellis perennis* administrated rats spent more of the time to find the platform. In conclusion, *Bellis perennis* may produce biphasic effects on both anxiety-like behaviour and learning performance of the rats[103]. The effect of *Bellis perennis* was investigated on viability of healthy neuronal cell line. On treatment with 90% alcohol, the cell viability was significantly decreased to 18% as compared to the negative control (only media) which was taken as 100%. The effect of alcohol was neutralized by *Bellis perennis* at 2μl/ml, 4μl/ml and 8μl/ml. It significantly increased the cell viability [104].

**Benincasa hispida**
The anxiolytic effects of alcoholic extract of *B. hispida* were evaluated in mice using elevated plus maze and light-dark transition test and spontaneous motor activity measured by actophotometer. The oral administration of the extract increased the percentage of time spent and the percentage of open arm entries in the elevated plus maze, as well as increase the time spent in the illuminated side of the light-dark test. The same extract was not able to modify the spontaneous motor activity measured in actophotometer [105].

The methanolic extract of *Benincasa hispida* exhibited significant anti-compulsive effect in marble-burying behavior test in mice, the effect which may be attributed to the enhancement of serotoninergic function[106].

The methanolic extract of fruit of *Benincasa hispida* caused reduction in spontaneous motor activity with no muscle relaxant activity. It also significantly potentiated the barbiturate induced hypnosis, and showed significant antihistaminic activity[107].

The anticonvulsant properties of alcoholic extract of *Benincasa hispida* was studied on maximal electroshock test (MEST), pentylentetrazole and strychnine-induced seizures model in mice. The alcoholic extract of *Benincasa hispida* protected animals against maximal electroshock-induced convulsion and reduced the mean recovery time from convulsion. It also showed anticonvulsant activity against pentylentetrazole-induced convulsion and protected mice against strychnine-induced convulsions[108].

The antidepressant activity of the methanolic extract (50, 100, and 200 mg/kg, administered orally for 14 successive days) was tested in Swiss male albino mice in comparison with classical antidepressant drugs (imipramine 15 mg/kg, fluoxetine 20 mg/kg, and phenelzine 20 mg/kg). The methanolic extract of *B. hispida* showed significant antidepressant-like activity in mice probably by inhibiting MAO-A, and through interaction with dopaminergic, α1-adrenergic, serotoninergic, and GABAergic systems [109].

The juice of *Benincasa hispida* showed significant activity against symptoms of morphine withdrawal. The results showed that *Benincasa hispida* was active in preventing the development of morphine addiction and suppression of opioid withdrawal in animals[110].

The chronic treatment with the aqueous extract of *Benincasa hispida* pulp (400mg/kg bw) appeared beneficial in the management of colchicines-induced rat model of Alzheimer's disease. It was also increased antioxidants in different brain areas and increased the number of correct choices out of 10 daily trials and decreased latency time dose dependently [110-111].

**Brassica nigra**
The antiepileptic activity of methanolic extract of *Brassica nigra* seeds was investigated on maximal electroshock induced seizures (MES), Pentylene tetrozole (PTZ), Picrotoxin (PIC) and biccuculine induced seizures in mice. It was found that the extract (200 and 400 mg/kg, orally), significantly prolonged the onset of tonic seizures and reduced the duration of incidence of seizures in PTZ, PIC and biccuculine induced seizure models, while in MES model, the extract showed significant effect in
abolishing tonic hind limb extensions by inhibiting voltage dependant Na⁺ channels or by blocking glutaminergic excitation mediated by the N-methyl-D-aspartate (NMDA) receptor [112]. The anti-epileptic effect of the methanolic extract of *Brassica nigra* seeds (75, 150 and 300 mg/Kg; ip) was evaluated in pentylentetrazole (PTZ) - induced kindling in mice. The methanolic extract of *Brassica nigra* seed reduced the intensity and duration of seizure. In addition, the *Brassica nigra* extract increased the SOD and NO levels and decreased the MDA level in the brain tissues[113].

**Bryophyllum calycinum**

The methanolic extract of *Bryophyllum calycinum* Salisb showed neuro-pharmacological effects in experimental animals (rats and mice). The fraction produced alteration of behavior pattern, caused dose-dependent potentiation of pentobarbitone sleeping time and had significant analgesic activity and possesses a potent CNS depressant action. The saline leaf extract of *Bryophyllum calycinum* Salisb produced a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis, reduction of exploratory activities in the head-dip and evasion tests. Moreover, a dose-dependent muscle incoordination was observed in the inclined screen, traction and climbing tests in mice. The saline leaf extract produced a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis, reduction of exploratory activities in the head-dip and evasion tests and a dose-dependent muscle incoordination in the inclined screen, traction and climbing tests[114-116].

The CH₂Cl₂ /CH₃OH extract reduced seizures induced by pentylentetrazol, strychnine sulphate and thiosemicarbazide and increases in the latency period of seizures and reduced the duration of seizures induced by the three convulsive agents[115,117-118].

**Caesalpinia crista**

The dried seed kernels of *Caesalpinia crista* aqueous extract was examined as learning and memory enhancer. The memory retention in mice treated with 50mg/kg aqueous extract of dried seed kernels of *Caesalpinia crista* against scopolamine induced amnesia was found to be 33.09 % in radial arm maze task performance. However, the memory retention increased to 45.29% in mice treated with 150mg/kg (iv) of the same extract. Accordingly, the authors suggested that the extract could be beneficial to improve cognition in disorders like dementia and various neurodegenerative disorders [119].

Amyloid beta (A beta) is the major etiological factor implicated in Alzheimer's disease. The ability of *Caesalpinia crista* leaf aqueous extract was studied on the prevention of (i) the formation of oligomers and aggregates from monomers (Phase I: A beta(42) + extract co-incubation); (ii) the formation of fibrils from oligomers (Phase II: extract added after oligomers formation); and (iii) dis-aggregation of pre-formed fibrils (Phase III: aqueous extract added to matured fibrils and incubated for 9 days). The aggregation kinetics was monitored using thioflavin-T assay and transmission electron microscopy. The results showed that *Caesalpinia crista* aqueous extract was able to inhibit the A beta(42) aggregation from monomers and oligomers and also able to dis-aggregate the pre-formed fibrils [120].

The anticonvulsant effect of seed extract of *Caesalpinia crista* was investigated by pentylenetetrazole, maximal electro shock strychnine- and picrotoxin-induced convulsions models. Diazepam was used as a standard reference for all models except maximal electro shock model, wherein phenytoin was used as standard reference. Seed kernels of *Caesalpinia crista* were powdered and subjected to successive extraction with petroleum ether, ethanol, methanol and water. All the extracts were administered as suspension in 2% gum acacia in all the experiments. In pentylene tetrazole maximal electro shock, strychnine- and picrotoxin-induced convulsion models, the medium and high doses (600 and 800mg/kg) of the extract showed significant anticonvulsant activity [121].

The anxiolytic activities of seed extract of *Caesalpinia crista* in experimental animals, mice and rats were investigated by stair-case model, Three doses (400, 600 and 800mg/kg) showed a significant and dose dependent anxiolytic activity by increasing the number of steps climbed, without any significant effect on rearings by all the three doses. Similarly in EPM model medium, high doses, but not the low dose had significantly enhanced both number of entries and time spent in open arms and decreased in number of entries and time spent in closed arms. In Hole board model, medium and high doses 600 and 800mg/kg but not the low dose 400mg/kg had significantly enhanced the number, latency and the duration of head dipping but not the rearings. However in LDT model high doses 800mg/kg had significantly exhibited anxiolytic activity by increasing time spent, number of crossings in light compartment and decreased the time spent in dark compartment and decreased the number of rearings in both light and dark compartments. In OFT models, medium and high doses 600 and 800mg/kg but not the low dose 400mg/kg had significantly enhanced total locomotion, central locomotion, number of grooming but the immobility time has drastically reduced. All doses have not exerted any significant effect with rearing, defecation and urination. Moreover in Mirror-chamber model of anxiety, both medium and high doses 600 and 800mg/kg but not the low dose 400mg/kg had significantly reduced the time latency to enter into the mirror chamber and increased the number of entries and time spent in the chamber. These result
confirmed the anxiolytic activity of *Caesalpinia crista* [122].

*Caesalpinia crista* seed extracts were screened for adaptogenic activity using cold stress and swim endurance models. The seed coat as well as kernel extracts administered orally at a dose of 300mg/kg significantly increased the swim endurance time. The extracts also corrected hyperglycemia, the depletion in serum cortisol level, increased total leukocyte count, and controlling the hyperlipidemic condition associated with to stress [123].

The effects of *Caesalpinia crista* extract on gallamine-induced relaxation in rat tibial muscle contractility were studied via measurement of isometric-tension-anesthetized, 10-12-week-old, male rats. *Caesalpinia crista* extract administered intravenously (iv) increased twitch contractions in a dose-dependent manner. The ED_{50} value was 2.75 x 10^{-4} g/kg bw. Treatment with *Caesalpinia crista* extract or neostigmine, however, reversed the relaxation induced by either gallamine or puff adder venom. The authors concluded that *Caesalpinia crista* extract stimulates the muscle contractile activity via activation of the cholinergic mechanism [124].

The calcium dependency and the cholinergic effect of the leaf extract of *Caesalpinia crista* was studied in isolated pregnant rat myometrium preparations. The leaf extract of *Caesalpinia crista* increased the contractile force in the isolated strips in a concentration-dependent manner. The effects were comparable to those obtained with acetylcholine. Contractions induced by the leaf extract of *Caesalpinia crista* or acetylcholine were inhibited in the presence of atropine. The stimulating action of the leaf extract of *Caesalpinia crista* on the contractile responses of isolated myometrium preparations may be mediated by cholinergic receptors. In calcium-free solution, the leaf extract of *Caesalpinia crista* induced a tonic contraction (contracture) of the muscle. Moreover, in high-potassium calcium-free solution the leaf extract of *Caesalpinia crista* caused contracture of the uterine smooth muscle. The leaf extract of *Caesalpinia crista* was still able to elicit contractions in calcium-free solution containing EDTA or EGTA. These findings refer to the existence of cholinergic receptors sensitive to the leaf extract of *Caesalpinia crista* which could influence the influx of calcium (phasic contraction) and mobilization of calcium from cellular stores (tonic contraction), both of which are responsible for the increase of contractile activity and development of the contracture of uterine smooth muscle [125].

*Caesalpinia crista* extract also caused concentration-dependent inhibition of spontaneous and high K^+ (80 mM)-induced contractions of isolated rabbit jejunum preparations, similar to that caused by verapamil [126].

*Calendula officinalis*

The neuroprotective effect of *Calendula officinalis* Linn. flower extract (COE) on Monosodium glutamate (MSG)-induced neurotoxicity was evaluated in rats. Adult Wistar rats were administered systemically for 7 days with MSG and after 1h of MSG injection, rats were treated with COE (100 and 200 mg/kg) orally. At the end of the treatment period, animals were assessed for locomotor activity and were sacrificed; brains were isolated for estimation of LPO, GSH, CAT, TT, GST, Nitrite and for histopathological studies. MSG caused a significant alteration in animal behavior, oxidative defense (raised levels of LPO, nitrite concentration, depletion of antioxidant levels) and hippocampal neuronal histology. Treatment with COE significantly attenuated behavioral alterations, oxidative stress, and hippocampal damage in MSG-treated animals [127].

The neuroprotective effect of *Calendula officinalis* flower extract (COE) on 3-NP-induced neurotoxicity in rats was evaluated by observing behavioral changes, OS and striatal damage in rat brain. Adult female Wistar rats were pretreated with vehicle or COE (100 and 200 mg/kg) for 7 days, followed by cotreatment with 3-NP (15 mg/kg, intraperitoneally) for the next 7 days. At the end of the treatment schedule, rats were evaluated for alterations in sensory motor functions and short-term memory. Animals were sacrificed and brain homogenates were used for the estimation of lipid peroxidation (LPO), glutathione, total thiols, glutathione S-transferase, catalase and nitrite. A set of brain slices was used for the evaluation of neuronal damage in the striatal region of the brain. 3-NP caused significant alterations in animal behavior, oxidative defense system evidenced by raised levels of LPO and nitrite concentration, and depletion of antioxidant levels. It also produced a loss of neuronal cells in the striatal region. Treatment with COE significantly attenuated behavioral alterations, oxidative damage and striatal neuronal loss in 3-NP-treated animals [128].

*Calendula officinalis* saponosides extracts have mild sedative effects and synergistic effects with sedative medications such as barbiturates [129]. Aqueous alcoholic extract of florets also showed CNS inhibitory effect with marked sedative activity in experimental animals [130].

*Calotropis procera*

The anticonvulsant activity of different root extracts of *Calotropis procera* was studied in rats using seizures induced by maximal electroshock seizures (MES), pentylentetrazol (PTZ), lithium-pilocarpine and electrical kindling seizures. In the MES test, the chloroform extract of *Calotropis procera* roots showed the most significant (P<0.01) anticonvulsant effect, it decreased the duration of hind limb extension (extensor phase), clonus and also the duration of the stupor phase compared with the controls. In the PTZ test, the chloroform extract exhibited a highly significant
(P<0.001) effect, and the aqueous extract had a significant (P<0.01) effect compared with the controls by delaying the onset of convulsions. The extracts also inhibited convulsions induced by lithium-pilocarpine and electrical kindling [131].

**Capsella bursa-pastoris**

The plant induced CNS-depressant action in mice which demonstrated by potentiation of barbiturate-induced sleeping time [138].

**Carum carvi**

The aqueous extract of *Carum carvi* was evaluated for antistress activity in normal and stress induced rats. The extract was studied for nootropic activity in rats and *in vitro* antioxidant potential to be correlated with its antistress activity. For the evaluation of antistress activity groups of rats were subjected to forced swim stress one hour after daily treatment of *Carum carvi* extract. Urinary vanillylmandelic acid (VMA) and ascorbic acid were selected as non invasive biomarkers to assess the antistress activity. The 24 h urinary excretion of vanillylmandelic acid (VMA) and ascorbic acid was determined in all groups under normal and stressed conditions. The nootropic activity of the extract as determined from acquisition, retention and retrieval in rats was studied by conditioned avoidance response using Cook’s pole climbing apparatus. Daily administration of *Carum carvi* at doses of 100, 200 and 300 mg/kg body weight one hour prior to induction of stress inhibited the stress induced urinary biochemical changes in a dose dependent manner. However no change in the urinary excretion of VMA and ascorbic acid was observed in normal animals. The cognition, as determined by the acquisition, retention and recovery in rats was observed to be dose dependent. The *in vitro* antioxidant activity was determined based on the ability of *Carum carvi* to inhibit lipid peroxidation in liver and brain homogenates. The extract produced significant inhibition of lipid peroxide formation in comparison with ascorbic acid in a dose dependent manner in both liver and brain [133].

**Carthamus tinctorius**

Subcutaneous administration of 1–10 g/kg bw of an aqueous or 50% methanol extract of the flowers had central nervous system depressant effects and relaxed skeletal muscles in mice. Subcutaneous administration of 10 g/kg bw of a 50% methanol extract of the flowers inhibited pentylentetrazole-induced convulsions in mice [134].

The effect of safflower or its isolate on functionally regulating monoamine transporter was studied using *in vitro* screening cell lines. Safflower insoluble fraction significantly inhibited serotonin uptake in Chinese hamster ovary cells stably expressing serotonin transporter (i.e. S6 cells). The active compound was isolated as coumaroylspermidine analog N(1),N(5)-(Z)-N(10)-(E)-tri-p-coumaroylspermidine. This compound potently and selectively inhibited serotonin uptake in S6 cells or in synaptosomes, with IC50 of 0.74±0.15 microM for S6 cells or 1.07±0.23 microM for synaptosomes and with a reversible competitive property for the 5HT-uptake inhibition. The potency of it for 5HT uptake was weaker than that of fluoxetine, whereas efficacy generally similar for both. Animals treated with this testing compound showed a significant decrease in synaptosomal 5HT uptake capacity [135-136].

All solvent-extracted Safflower (HH) fractions, in different degrees, markedly increased both dopamine uptake by Chinese hamster ovary (CHO) cells stably expressing dopamine transporter (DAT) and norepinephrine uptake by CHO cells expressing norepinephrine transporter (NET), and also showed that chloroform (HC), ethyl acetate (HE), and n-butyl alcohol extract strikingly depressed serotonin uptake by CHO cells expressing serotonin transporter (SERT); wherein, the potencies of ethanol extract, HC, HE, and aqueous extract to up-regulate dopamine/norepinephrine uptake and potency of HE to inhibit serotonin uptake were relatively stronger. Further investigation revealed that the enhancement of dopamine/norepinephrine uptake by HC and HE was dependent of DAT/NET activity, and the HE-induced inhibition of serotonin uptake was typical of competition [137].

The neuroprotective properties of Hydroxysafflower yellow A (HSYA) on neurotoxicity of glutamate in primary cultured rat cortical neurons along with its possible mechanism of action were examined. The excitotoxic neuronal death was attenuated markedly by HSYA treatment. HSYA decreased expression of Bax and rescued the balance of pro-and anti-apoptotic proteins. In addition, HSYA significantly reversed up-regulation of NR2B-containing NMDA receptors by exposure to NMDA, while it did not affect the expression of NR2A-containing NMDA receptors [138].

The neuroprotective efficacy of the combination of (astragali, ligusticum wallichii, angelica sinensis and *Carthamus tinctorius*) on mitigating brain infarction and global ischemia as well as preventing the neurodegeneration following ischemia was studied. They improved cerebral blood circulation, which refer to a potential to alleviate the symptoms of degenerative diseases, Alzheimer’s disease and Parkinson’s disease [139].

The neuroprotective effects of hydroxysafflower yellow A (HSYA) on cerebral ischemic injury in both *in vivo* and *in vitro* were studies. In *in vivo* experiment, male Wistar-Kyoto (WKY) rats with middle cerebral artery occlusion (MCAO) were evaluated for neurological deficit scores followed by the treatment with a single dose of HSYA. Furthermore, the infarction area of the brain was assessed in the brain slices. In *in vitro* experiment, the
effect of HSYA was tested in cultured fetal cortical cells exposed to glutamate and sodium cyanide (NaCN) to identify its neuroprotection against neurons damage. The results of in vivo study showed that sublingular vein injection of HSYA at doses of 3.0 mg/kg and 6.0 mg/kg exerted significant neuroprotective effects on rats with focal cerebral ischemic injury by significantly decreasing neurological deficit scores and reducing the infarct area compared with the saline group, HSYA at a dose of 6.0 mg/kg, gave a similar potency as nimodipine at a dose of 0.2 mg/kg. Sublingular vein injection of HSYA at the dose of 1.5 mg/kg showed a neuroprotective effect, however, with no significant difference when compared with the saline group. In vitro results showed that HSYA significantly inhibited neuron damage induced by exposure to glutamate and sodium cyanide (NaCN) in cultured fetal cortical cells, however, the neuroprotective action of HSYA on glutamate-mediated neuron injury was much better than that of HSYA on NaCN-induced neuron damage [140].

Free radical scavenging activity of the extracts of petals (bud, early stage, full blooming and ending stage), leaf, stem, root and seeds of Mogami-benibana (Carthamus tinctorius), the contents of the major active components of carthamin and polyphenols, and neuroprotective effect of the petal extracts and carthamin in the brain of mice and rats were examined. Water extracts of Mogami-benibana petals scavenged superoxide, hydroxyl and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and singlet oxygen. There was also a relationship between DPPH radical scavenging activity and carthamin content in the petal extracts of safflower[141].

The potential protective effect of Hydroxysafflor Yellow A (HSYA) in spinal cord ischemia/ reperfusion (I/R) injury was studied in rabbits. Neurological outcomes in HSYA group were slightly improved compared with those in I/R group. Histopathological analysis revealed that HSYA treatment attenuated I/R induced necrosis in spinal cords. Similarly, alleviated oxidative stress was indicated by decreased malondialdehyde (MDA) level and increased superoxide dismutase (SOD) activity after HSYA treatment. Moreover, HSYA also protected neurons from I/R-induced apoptosis in rabbits as seen from TUNEL results[142].

The probable attenuating effect of Hydroxysafflor yellow A (HSYA) on brain injury induced by lymphostatic encephalopathy (LE) was investigated in rats. Heart rate variability (HRV) was used as an indirect measurement of the regulatory function of the autonomic nervous system by recording the ECG signals from rats. It was shown that treatment with HSYA (5 mg/kg, ip) significantly alleviated the neurological deficits observed in rats with LE. Histological staining revealed that HSYA treatment attenuated LE-induced cell apoptosis in the rostral ventrolateral medulla (RVLM). Animals in the LE groups exhibited impaired regulatory roles of the autonomic nervous system in cardiovascular function, which was suppressed by pretreatment with HSYA. Additionally, HSYA administration significantly prevented the decrease of endothelial nitric oxide synthase (eNOS) mRNA and protein expression in the RVLM of rats with LE. Accordingly, HSYA might provide neuroprotection against LE-induced brain injury and the associated functional alterations, which is likely regulated by the nitric oxide pathway[143].

The therapeutic effects of hydroxysafflor yellow A (HSYA) on focal cerebral ischemic injury in rats and its related mechanisms have been investigated. Focal cerebral ischemia in rats were made by inserting a monofilament suture into internal carotid artery to block the origin of the middle cerebral artery and administrated by HSYA via sublingular vein injection in doses of 1.5, 3.0, 6.0 mg /kg at 30 min after the onset of ischemia, in comparison with the potency of nimodipine at a dose of 0.2 mg/kg. Then, 24 h later, the evaluation for neurological deficit scores of the rats were recorded and postmortem infarct areas were determined. HSYA dose-dependently improved the neurological deficit scores and reduced the cerebral infarct area, and HSYA bore a similarity in potency of the therapeutic effects on focal cerebral ischemia to nimodipine. The inhibition rates of thrombosis formation by HSYA at the designated doses were 20.3%, 43.6% and 54.2%, respectively, compared with saline-treated group. Inhibitory activities of HSYA were observed on ADP-induced platelets aggregation in a dose-dependent manner, and the maximum inhibition of aggregation of HSYA was 41.8%. HSYA provided a suppressive effect on production of TXA2 without significant effect on plasma PGI2 concentrations. Blood rheological parameters were markedly improved by HSYA, such as whole blood viscosity, plasma viscosity, deformability and aggregation of erythrocyte, but no significant effect for HSYA on homatocrit was found[144].

The effects of Carthamus tinctorius was evaluated on bcl-2, caspase-3 expression of apoptosis of neurons. The middle cerebral artery of rats was occluded for 2h by inserting an intraluminal molofilament, and reperfusion was then instituted for 4h or 22h. All treated groups at different times decreased the volume of infarction (P<0.05), while large-dose group showed more distinct decrease than other groups (P<0.05). All treated groups at different times increased bcl-2 and decreased caspase-3 expression as well, while, large-dose group showed more distinct effect (P<0.05) [145].

The effect of Hydroxysafflor yellow A (HSYA) on mitochondrial permeability transition pores (mPTP) was studied in the rat brain. HSYA at 10-80 micromol/l inhibited Ca2+- and H2O2-induced swelling of mitochondria isolated from rat brains. The addition of Ca2+ generated reactive oxygen species (ROS) in isolated mitochondria, the effect which inhibited by HSYA (10-80
micromol/l). At the same time, HSYA significantly improved mitochondrial energy metabolism, enhanced ATP levels and the respiratory control ratio [146].

**Cassia occidentalis**

The antianxiety and antidepressant activity of the ethanolic and aqueous extracts of *Cassia occidentalis* leaves (500 mg/kg, orally) was evaluated in rodents. Antianxiety activity was tested by exposing rats to unfamiliar aversion in different methods like elevated plus maze model and actophotometer. In elevated plus-maze test, the ethanolic and aqueous extracts of *Cassia occidentalis* leaves at a dose of 500 mg/kg orally, significantly increased the number of entries and time spent into the open arm. The magnitude of the antianxiety effects 500 mg/kg orally, of ethanolic and aqueous extracts of *Cassia occidentalis* was comparable to that of diazepam 5 mg/kg ip. The average of basal activity scores after 30 and 60 min of administration of ethanolic and aqueous extracts of *Cassia occidentalis* leaves 500 mg/kg orally, showed significant reduction of the locomotor activity. The antidepressant activity was tested by using despair swim test and tail suspension test. In despair swim test apparatus, the ethanolic and aqueous extracts of leaves of *Cassia occidentalis* at a dose of 500 mg/kg orally, significantly decreased the immobility time. The magnitude of the antidepressant effects of 500 mg/kg orally, of ethanolic and aqueous extracts of leaves of *Cassia occidentalis* was comparable to that of fluoxetine 10 mg/kg ip. In tail suspension test, the ethanolic and aqueous extracts of leaves of *Cassia occidentalis* at a dose of 500 mg/kg orally, significantly decreased the immobility time. The magnitude of the antidepressant effects of 500 mg/kg orally, of ethanolic and aqueous extracts of *Cassia occidentalis* was comparable to that of fluoxetine 10 mg/kg ip. Ethanolic extract of *Cassia occidentalis* leaves showing more significant antidepressant activity over the aqueous extract [147].

Geriforte, a combination of several plant ingredients (including *Cassia occidentalis*) is being used in India as a restorative tonic in old age. This preparation was evaluated for anti-stress (adaptogenic) activity by inducing various stressful situations in animals. The survival time of swimming mice increased with different doses of Geriforte. The drug also prevented changes in adrenals (increase in weight and reduction of ascorbic acid and cortisol contents) induced by stress (5 hr swimming). Both restrain and chemically-induced ulcers were prevented by 100 mg/kg of Geriforte. Furthermore, pretreatment with Geriforte prevented the increase of liver weight and volume induced by carbon tetrachloride and also the milk-induced leucocytosis. Gradual and constant increase in body weight was observed in the rats taking the drug. However, no effect was observed on spontaneous motor activity and body temperature. It has some central nervous system stimulant activity as judged by the reduction of hexobarbital sleeping time. The LD₅₀ as determined in acute toxicity studies on mice was between 5-6 g/kg orally [148].

**Centaurea cyanus**

Moschamine a safflomide-type phenylpropenoic acid amide found in *Centaurea cyanus*, was tested as antiserotonergic agent. At the concentration of 10 µmol/l, moschamine was able to inhibit forskolin-stimulated cAMP formation by 25% (p < 0.015), via inhibiting serotonin receptors in the OK cells. The inhibition was repressed by two 5-HT1 antagonists (Nan-190 and spiperone), suggesting that moschamine may suppress cAMP formation via binding to 5-HT1 receptors in the cells [149].

**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, skeletal muscle relaxant effect, decreasing of morphine and nicotine withdrawal and other CNS effects.

**REFERENCES**

1. 1- Al-Snafi AE. Central nervous and endocrine effects of Myristica fragrans. 4th Arabic Conf. of Medicinal plants, Thamar Univ, Yemen, 15, 1999, 111-121.
44. Al-Snafi AE. The chemical constituents and pharmacological effects of Chenopodium album- An overview. *International J of Pharmacological Screening*, 2, 2015, 63.
46. Al-Snafi AE. Encyclopediaof the constituents and pharmacological effects of Iraqi medicinal plants. Thi qar University, 2013.


149. Park J B. Synthesis, biological activities and bioavailability of moschamine, a safflomide-type phenylpropenoic acid amide found in *Centaurea cyanus*. *Natural Product Research: Formerly Natural Product Letters*, 26(16), 2012, 1465-1472.