



A Review: Herbal Plants as Probable Anti-Stress Agents

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Abstract

Stress disorders became more prevalent in the modern era. Therefore, this must be addressed by employing natural and synthetic treatment approaches. Herbal therapies are the best preferred nutraceutical for treatment of stress disorders in current era. This approach may overcome few side effects like cardio toxicity, sexual dysfunction, sleep disorders etc. which is otherwise evident in synthetic drugs. Some herbal plants which are rich in flavonoids are studied for probable anti stress activity. Flavonoids are major source of antioxidants which helps in alleviation of neurological disorders which are characterized by production of free radicals and their destruction in CNS. These agents are experimented with the help of rodent animal models like rats and mice. The animals are induced with CUMS by exposing them to several stress stimuli. CUMS is a rodent paradigm which leads to oxidative stress and thereby neurological damage. After inducing CUMS, they are dosed with standard drug and test drug of different doses followed by assessment of behavioral and biochemical parameters.

Keywords: Anti-stress, CUMS, flavonoids, herbal plants.

Introduction

Stress is characterized by clinical signs like anxiety, insomnia, and physical and psychological trauma. Stress is a noxious factor that causes a decrease in the functioning of noradrenergic, dopaminergic, and serotonergic systems. They cause the production of free radicals in the brain and hyperactivity of HPA (hypothalamic-pituitary axis) and increase the levels of BDNF and other inflammatory cytokines in CNS. Activation of HPA causes increased

production of ACTH and thereby increases levels of corticosterone in the blood. The study of pathophysiology and screening of antistress agents is done with the help of CUMS (chronic unpredictable mild stress) induced rodent models. CUMS is a rodent stress paradigm that produces stress symptoms like that in humans. CUMS is produced by subjecting animals to different stress-inducing stimuli. Subsequently, test agents are administered and screened for behavioral and biochemical indices. Synthetic drugs are available in the market for treating

stress disorders. However, they cause adverse effects on other organ systems on prolonged exposure. Therefore, it is essential to introduce herbal plants which could overcome the limitations of synthetic drugs available in the market. A few drugs are listed below which are potential antistress agents¹.

2. List of herbal plants as probable antistress agents

2.1 *Perilla frutescens*

Leaves of *Perilla frutescens* is used for centuries as vegetable and plant-based medicine in East Asian countries. This plant is used as antioxidant², antidepressant³, anti-inflammatory and antimicrobial⁴. Essential oils are extracted from leaves by steam distillation. Essential oils of *Perilla frutescens* (EOPF) contain various phytochemicals like perilla aldehyde, perilla ketone, limonene, safrole, protocatechuic acid, etc.⁵. Studies found that EOPF attenuated depressive disorder in mice. Mice are exposed to stress paradigms for five weeks followed by administration of standard drug Fluoxetine and test drugs of doses 3, 6 and 9 mg/kg for next three weeks. Subsequently behavioral and biochemical indices were assessed. Behavioral tests include Sucrose Preference Tests (SPT), Tail Suspension Test (TST) and Forced Swimming Test (FST). Biochemical tests include measurement of 5-HIAA levels in hippocampus, levels of inflammatory cytokines like TNF- α , BDNF and interleukin. EOPF significantly decreased immobility, increased sucrose consumption but the effect was not dose dependent⁶. The drug also decreased the levels of 5-HIAA, interleukin, TNF- α and BDNF. Therefore, it is concluded that EOPF administration caused significant

antidepressant effects in CUMS induced mice⁷.

2.2 *Gardenia jasminoides*

Gardenia jasminoides (Cape Jasmine) although native to China⁸ it is also found in Japan, Vietnam, Taiwan, Sri Lanka, etc. The plant is a woody, evergreen shrub with broad leaves. It is used to treat diabetes, inflammation (Zhang et al., 2022), liver disorders^{10, 11} etc. The plant contains phytochemicals like geniposide, gardenoside, crocin, triterpenoids, myristic acid, etc.¹²⁻¹⁴. Geniposide is the major component that has been found to contain neuroprotective activity. The rats are the models for elucidation of antistress screening of this phytochemical. CUMS was induced for consecutive three weeks along with dosing at three different concentrations (25, 50, and 100 mg/kg). behavioral tests include SPT, OFT, FST¹⁵⁻¹⁷. Assessment of HPA hyperactivity include evaluation of levels of serum CORT, ACTH, and CRH mRNA expression. Geniposide treatment at doses 25, 50, 100mg/kg altered behavioral deficits by increasing sucrose consumption and decreasing immobility period in FST and OFT. The drug also altered HPA hyperactivity by reducing serum CORT and ACTH levels and reduced expression of hypothalamic CRH mRNA expression¹⁸. Moreover, no significant effect on ACTH serum levels was found. Thus, geniposide was found to possess a mighty antidepressant effect by mediating its effects on HPA axis¹⁹.

2.3 *Hemerocallis citrina Baroni*

Hemerocallis citrina Baroni (HC) is a conventional herbal medicine which belongs

to the East-Asian regions. The plant contains flavonoids²⁰ polyphenols, caffeic acid derivatives, etc.²¹ They are used to treat several ailments like insomnia, and cancer and possess hepatoprotective²² and antioxidant properties²³ The study is conducted to assess the potential antidepressant effect regarding its improvement in cognition. The study employed CUMS induced rat models. The phenolic extract of this plant is screened for the activity. The extraction was carried out with the help of 80% ethanol by cold-dipping method²⁴ induced rats were treated with test drug of doses 10, 20, 40 mg/kg per day. The mechanism of action was evaluated by assessing the levels of CORT, BDNF, monoamine neurotransmitters and levels of oxidative stress^{25, 26} Behavioral tests include SPT²⁷ and cognitive effects were assessed by employing the Morris water maze test²⁸ Monoamine neurotransmitter levels were assessed with the help of UPLS-MS²⁶. The serum CORT and BDNF in the hippocampus were assessed with the help of enzyme-linked immunosorbent assay (ELISA) kits. HCPE at 40mg/kg improved cognitive deficits. The herb also attenuated oxidative stress and increased the levels of neurotransmitters²⁹. Therefore, it was concluded that HCPE could attenuate cognitive and emotional disorders and management of oxidative stress in the CNS³⁰.

2.4 Cystisus scoparius

Cystisus scoparius is a plant found in Nilgiris region. The plant was shade dried and powdered coarsely. Then they are subjected to maceration with 60% methanol for 72 hours at room temperature³¹. The filtrate thus obtained was dried with the help of rotary

vacuum evaporator under reduced pressure. Rats were subjected to CUMS for 21 days and dosed with standard drug diazepam of dose 2mg/kg peroral and extract of doses 125 mg/kg and 250mg/kg. The effect was screened by behavioral and biochemical evaluations. Behavioral evaluation was done to detect behavioral deficits which include OFT. Biochemical evaluations include assessment of endogenous antioxidants such as catalase (CAT) and superoxide dismutase (SOD), ascorbic acid, Thio barbituric acid reactive substances in brain, kidneys and adrenal glands. CS significantly decreased immobility period and improved the levels of endogenous antioxidants. Therefore, it is suggested that the plant possess antistress and antioxidant effects^{32, 33}.

2.5 Hibiscus sabdariffa

Hibiscus sabdariffa is a Chinese herbal medicine which acts as aphrodisiac, antiseptic³⁴ astringent, digestive³⁵, etc. The drug is also a remedy for bilious conditions, cancer, cough, hypertension³⁶, neurosis, scurvy, inflammation³⁷ etc. The herb eradicates oxidative stress by improving the levels of endogenous antioxidants and monoamine levels in the brain³⁸. The study aims at finding out the underlying mechanism which contributes to the antidepressant effect. The plant contains PCA (protocatechuic acid) which will be screened. PCA was extracted from Hibiscus sabdariffa by employing solvent extraction technique³⁹. The extract is screened with the help of CUMS induced mice models. Mice were induced with CUMS for 4 weeks and simultaneously dosed with standard drug fluoxetine and extract of doses 100mg/kg and 200mg/kg for 24 days.

Behavioral tests include FST, SPT, OFT and biochemical tests include evaluation of serum levels of CORT, endogenous antioxidants, inflammatory cytokines, etc. PCA improved sucrose preference, decreased immobility time, decreased levels of inflammatory cytokines and improved antioxidant defense systems. In conclusion, PCA was found to be potent antistress agent by exerting its effects against oxidative stress¹.

2.6 *Lepidium meyenii*

Lepidium meyenii is an herbal medicine found in Peru that exhibits anxiolytic and antidepressant effects. The study evaluated the behavior and biochemical parameters of the drug with the help of CUMS induced mice models. The drug is extracted with petroleum ether. The plant consists of several phytochemicals like glucosinolates, macamides, macaenes, and alkaloids⁴⁰. In this study, mice were induced with CUMS for six weeks followed by administration of the standard drug fluoxetine and test drugs at three different doses to mice groups assigned for the same. The extract exhibited a significant reduction in serum levels of corticosterone. The drug also elevated the levels of neurotransmitters like noradrenaline and dopamine in the brain. Duration of immobility decreased in tail suspension test post administration of the extract. The antidepressant effect of herbal plant is thus established owing to its effects on oxidative stress and effects on dopaminergic and noradrenergic systems in the CNS⁴¹.

2.7 *Panax notoginseng*

Panax notoginseng is a conventional Chinese herbal medicine used for treatment of several

ailments associated with CVS. The plant consists of phytochemicals like saponins, amino acids, polyacetenes polyacetylenes, volatile oils, polysaccharides and flavonoids⁴². The study found that the antidepressant activity is majorly attributed to saponins present in them. The CUMS mice models are used for assessment of pharmacology of test drug. Mice are assessed with different behavioral tests and evaluation done on ventral prefrontal cortex and hippocampal slices of mouse brain for expression of circular RNA protein. This RNA protein is responsible for expression and synthesis of cAMP response element binding protein1 (CREB1) and BDNF. This evaluation was done with the aid of high-through sequencing and confirmed by qRT-PCR. Consequently, assessment of levels of BDNF and CREB1 were done by western blotting. The plant extract regulated the extent of circular RNA thereby regulating the levels of BDNF and CREB1. Immobility period decreased in FST and TST. This affirms the antidepressant action of plant *Panax notoginseng*⁴³.

2.8 *Helicid nilgirica*

Helicid is a bioactive constituent of herb *Helicid nilgirica* which is one of the Chinese herbal medicines used to treat the chronic unpredictable stress disorder and neuropathic pain⁴⁴. However, the mechanism behind alleviation of CUMS like symptoms was still being the question. The compound has been investigated for the effect of *Helicid* on CUMS rat models. Rats were subjected to 6 weeks stress paradigms leading to CUMS like symptoms which include decrease in body weight and sucrose preference; significantly increased immobility in OFT. *Helicid* notably

regulated the serum levels of corticosterone and inflammatory cytokines. The drug countermanded depressive like disorders like fluoxetine. The antidepressant action is exhibited by helicid through serotonergic systems. Therefore, Helicid is a potent antidepressant⁴⁵.

2.9 Polygonum avicularia

Polygonum avicularia is one of the folkloric medicines of Mediterranean coastal areas of Egypt. Plants contain phytochemicals like saponins, flavonoids, alkaloids and sesquiterpenes⁴⁶. The plant is used as remedy for cough, bronchitis, piles, hemorrhages and diarrhea. The plant is also used for treating gingivitis and UTIs. Avicularin is a flavonoid extracted from the plant *Polygonum avicularia* with the help of 70% ethanol⁴⁷. This extract was screened for probable antistress activity. The mice were induced with CUMS followed by administration with standard (fluoxetine) and test drugs to different mice groups assigned. Consequently, behavioral and biochemical parameters were assessed. Behavioral tests include sucrose preference test, forced swimming test, tail suspension test and biochemical tests are done with the help of ELISA kit which include assessment of BDNF, TNF- α and interleukin. Results revealed that avicularin massively reduced depressive like effects in mice. Improvement observed behaviorally like reduction in immobility time and increased sucrose preference. The drug also reduced the rate of apoptosis in hippocampal slides of mouse brain. Therefore, it is concluded that avicularin acts as antidepressant in CUMS induced mice models⁴⁸.

Conclusion

Owing to the physiological functions established from preclinical/ non-clinical data, we can conclude that herbal plants contain probable antistress activity. However, the term "probable" is still in existence due to lack of clinical data. Only a well-established clinical data can confer assurance of introducing herbal formulations to the market for aforesaid activity.

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