A review on antidepressant plants

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Abstract

Depression is a heterogeneous mood disorder that has been classified and treated in a variety of ways. Although a number of synthetic drugs are being used as standard treatment for clinically depressed patients, they have adverse effects that can compromise the therapeutic treatment. Thus, it is worthwhile to look for antidepressants from plants with proven advantage and favourable benefit-to-risk ratio. A number of medicinal plants *per se* and medicines derived from these plants have shown antidepressant properties by virtue of their medicinal constituents. The causes of depression are decreased brain levels of monoamines like noradrenaline, dopamine and serotonin. Therefore, drugs restoring the reduced levels of these monoamines in the brain either by inhibiting monoamine oxidase or by inhibiting reuptake of these neurotransmitters might be fruitful in the treatment of depression. The present review is focused on the medicinal plants and plant-based formulations having antidepressant activity in animal studies and in humans.

Keywords: Depression, Medicinal plants, Antidepressants, Herbal medicine.

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Introduction

Mental depression is a chronic illness that affects a person's mood, thoughts, physical health and behaviour. Symptoms of depression include biological and emotional components. Biological symptoms include retardation of thought and action, loss of libido, sleep disturbance and loss of appetite. Emotional symptoms include misery, apathy and pessimism, low self-esteem consisting of feeling of guilt, inadequacy and ugliness, indecisiveness and loss of motivation. There are two types of mental depression, namely unipolar depression, in which mood swings are always in the same direction and is common (about 75% of cases), non-familial, clearly associated with stressful life events, and accompanied by symptoms of anxiety and agitation. The second type is bipolar depression (about 25% of cases), sometimes also called as endogenous depression, shows a familial pattern, unrelated to external stresses and usually appears in early adult life, and is much less common, results in oscillating depression and mania over a period of a few weeks[1]. Patients with depression have symptoms that reflect decrease in brain monoamine neurotransmitters, specifically norepinephrine, serotonin and dopamine[2]. Reserpine, an antihypertensive drug, isolated from ***Rauvolfia serpentina* Benth. ex Kurz**, that depleted neuronal storage granules of norepinephrine, serotonin and dopamine, produced clinically significant depression in 15% or more of patients[3].

Prevalence rate for all mental disorders in India was observed to be 65.4/1000 population. Out of which prevalence rate for affective disorders is estimated to be 31.2/1000 population[4]. Depression is the leading cause of disease-related disability among women in the world today. Depression is much more common among women than men, with female/male risk ratios roughly two : one[5]. The prevalence of major depression is estimated to be 2% in the general population over 65 years of age[6]. About 11.2% school dropouts had severe to extreme grades of depression as against 3% among school going and nil among college going adolescents[7].

Although a number of synthetic drugs are being used as the standard treatment for clinically depressed patients, they have adverse effects that can compromise the therapeutic treatment. These common adverse effects include dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety agitation, drowsiness, and cardiac arrhythmias. Several drug-drug interactions can also occur. These conditions create an opportunity for alternative treatment of depression by use of medicinal plants or by plant-based antidepressant formulations.

Medicinal plants as antidepressants

The plants proved to possess antidepressant property are: ***Hypericum perforatum* Linn.**, ***Areca catechu* Linn.**, ***Bacopa monnieri* (Linn.) Penn.**, ***Centella asiatica* (Linn.) Urban**, ***Clitoria ternatea* Linn.**, ***Cimicifuga racemosa* (Linn.) Nutt.**, ***Crocus sativus* Linn.**, ***Curcuma longa* Linn.**, Evening Primerose (***Oenothera*** spp.) oil, ***Ginkgo biloba* Linn.**, ***Magnolia officinalis* Rehder & E. H. Wilson**, ***Mimosa pudica* Linn.**, ***Ocimum sanctum* Linn.**, ***Withania somnifera* Dunal**, ***Piper methysticum* G. Forst.** (Kava Kava, ***Siphocampylus verticillatus* (Cham.) G. Don**, ***Rhazya stricta* Decne**, ***Apocynum venetum* Linn.**, ***Morinda officinalis* How**, ***Perilla frutescens* (Linn.) Britton**, and ***Rhizoma acori tatarinowii.***

Cimicifuga racemosa

Clitoria ternatea

Curcuma longa

***Hypericum perforatum* Linn.** (Family-*Hypericaceae*)

It is better known as St. John's wort, has been used clinically for centuries[8]. It is a perennial herb distributed in Europe, Asia, North Africa and North America. Indian plant grows up to a height of 1m distributed in western Himalayas at an altitude of 1000-3500m. It has been known for centuries for its putative medicinal properties, including antidepressant, anxiolytic, diuretic, antibiotic, antimalarial, wound healing and anthelmintic[9, 10]. A standardized 50% aqueous ethanolic extract of Indian plant (100-200 mg/kg p. o.) once daily for 3 consecutive days showed significant antidepressant activity in behavioural despair test, tail-suspension test, learned helplessness test and reserpine induced hypothermia test in rats and mice. The observed antidepressant activity of Indian plant was qualitatively comparable to that induced by Imipramine[11, 12]. Indian plant has been shown to exert significant antioxidant activity induced by augmented activity of oxidative free radicals scavenging enzymes, superoxide dismutase, catalase and glutathione peroxide[13]. Hypericum extract, standardized to both hypericin and hyperforin, appears to have significant free radical scavenging properties in cell-free and human vascular systems[14]. These favourable effects were achieved with ***H. perforatum*** having the ability to treat both depression and amnesia with lower potential side effects[15]. Hypericum extract STW 3 administered once daily in a dose of 612 mg for up to 24 weeks produced antidepressant effect equivalent to Sertraline (50 mg) in patients of moderate depression[16]. Efficacy and tolerability of Hypericum LI 160 was comparable to fluoxetine in mild to moderate depression in a 4-week randomized, double-blind trial[17]. Thus, Hypericum extract can be effective in routine treatment of mild to moderate depressive disorders[18]. However, it was not effective for treatment of patients with major depression[19].

Methanol extracts of the aerial parts (blossom) of ***H. canariense* Linn.**, ***H. grandifolium* Choisy**, ***H. glandulosum* Gilib.** and ***H. reflexum* Linn. f.**, found in Canary Island, showed antidepressant-like effect in mice[20, 21]. Hypericum contains numerous compounds with documented biological activity. Constituents that have stimulated the most interest include the naphthodianthrones namely hypericin and

pseudohypericin[22]; phloroglucinols[23] namely hyperforin and adhyperforin; flavonoids[24] like flavonol glycosides, viz. rutin, quercitrin, isoquercitrin, hyperin/ hyperoside and aglycones, viz. kaempferol, luteolin, myricetin and quercetin; xanthones namely kielkorin in roots[25], 1,3,6,7-tetrahydroxyxanthone in trace amounts in leaves and stems[26]. Many pharmacological activities appear to be attributable to hypericin and to the flavonoid constituents. However, hyperforin has been considered as an important antidepressant constituent of ***H. perforatum***[27-29] and this may be involved in inhibition of uptake of serotonin, noradrenaline and dopamine[30, 31]. An increase of 5-HT level was also observed in hypothalamus and hippocampus. The action of Hypericum extract is consistent with the notion that serotonergic system is involved[32]. LI 160, standardized extract of ***H. perforatum*** and pure substance hypericin showed weak inhibitory effect on MAO-A and MAO-B. It also markedly inhibited the synaptosomal uptake of serotonin and noradrenaline. However, dopamine uptake and neuronal uptake of GABA and L-glutamate are also inhibited. These effects may mainly be attributed to hyperforin present in the extract[33, 34].

***Areca catechu* Linn.**
(Family-*Arecaceae*)

It is widely cultivated in India and Sri Lanka, South of China and Philippines, in Malaysia, Indonesia and Eastern Africa. Its nuts are being used by people for masticatory purposes in different parts of the world and it is a very popular chewing nut in the Indo-Pak subcontinent. It showed significant antidepressant activity in forced swim test and tail-suspension test in rodents[35, 36]. Alkaloids such as arecaidine, arecoline, and a few other constituents, reported to be present in areca nuts were found not to inhibit monoamine oxidase (MAO). On the other hand, dichloromethane fraction from areca nuts showed antidepressant activity via MAO-A inhibition[37].

***Bacopa monnieri* (Linn.) Penn.**
(Family- *Scrophulariaceae*)

It is commonly known as *Brahmi,* and is found in wet, damp and marshy places throughout India and subtropical region up to 1000 m elevation. It has been used as nervine tonic and also enhances learning and memory. The active constituents are the alkaloids, namely brahmine, herpestine and mixture of 3 other alkaloids and also saponins, namely, bacoside A and B. The standardized methanolic extract (20 and 40 mg/kg, p.o.) given once daily for 5 days showed significant antidepressant activity in forced swim test and learned helplessness models of depression and this effect was comparable to that of Imipramine[38].

***Centella asiatica* (Linn.) Urban**
(Family-*Apiaceae*)

The drug consists of dried aerial parts (preferably leaves). It is distributed throughout the tropical and subtropical regions of India. Total triterpenes from the plant reduced the immobility time of mice in forced swimming test and thus had antidepressant activity[39].

***Cimicifuga racemosa* (Linn.) Nutt.**
(Family-*Ranunculaceae*)

It is distributed in temperate Himalayas from Kashmir to Bhutan (2300-4000 m), Eastern Europe and Siberia. Ethanolic-aqueous extracts of ***C. racemosa*** (50 or 100 mg/kg) significantly decreased the period of immobility in tail suspension test in experimental animals and thus showed antidepressant activity[40].

***Clitoria ternatea* Linn.**
(Family-*Fabaceae*)

A cosmopolitan herb found in the tropics. Methanolic extract of plant decreased the duration of immobility in tail suspension test, thus possessing antidepressant activity via serotonergic system[41].

***Crocus sativus* Linn.**
(Family-*Iridaceae*)

Commonly known as Saffron, is indigenous to Greece, Asia Minor and Persia in which it grows wildly. It is also cultivated in Spain, France, Greece, Persia and India. Saffron at a dose of 30 mg/day TDS and BD was found to be effective similarly to Imipramine 100 mg/day (TDS) and Fluoxetine 20 mg/day (BD), respectively in the treatment of mild to moderate depression in adult patients[42,43].

***Curcuma longa* Linn.**
(Family-*Zingiberaceae*)

This plant commonly known as turmeric is native of Southern Asia,

cultivated in India, China and other tropical countries. The aqueous extracts administered orally to the mice from 140 to 560 mg/kg for 14 days, elicited dose-dependant reduction of immobility time in the tail suspension test and the forced swimming test in mice. Turmeric had significant antidepressant activity and this may be mediated in part through MAO-A inhibition in mouse brain[44].

Evening Primerose oil

Evening Primerose oil is the fixed oil obtained from the seeds of ***Oenothera*** species (Family-*Onagraceae*). The principle species cultivated in the UK is ***O. biennis*** **Linn.** Evening Primerose oil (0.2 ml/20 g) showed significant antidepressant effect on all days of treatment in mouse model of chronic fatigue syndrome (CFS) in which mice were forced to swim everyday for 7 days for 6 minutes session[45].

Ginkgo biloba **Linn.**
(Family-*Ginkgoceae*)

It is native of China and occasionally cultivated in Indian gardens, particularly on Hills. A few trees are found in Himachal Pradesh. Its extract (14 mg/kg, p.o.) restored restraint stress-induced elevation in whole brain levels of catecholamines (norepinephrine, dopamine) and serotonin[46]. The extract has a demonstrable effect in improving mood in healthy older volunteers[47]. The combination of ***G. biloba*** extract with Venlafaxine enhanced the protection of neurons and decreased damage to the brain, while relieving the side effects of synthetic antidepressants[48].

Magnolia officinalis **Linn.**
(Family- *Magnoliaceae*)

The tree is distributed in central and eastern Himalayas up to 1500m, Burma and Malay Peninsula. Acute treatments with active metabolites such as magnolol and dihydroxydihydromagnolol (50-100 mg/kg, i.p.) obtained from aqueous extract of the bark, attenuated the forced swim-induced experimental depression in mice[49].

Mimosa pudica **Linn.**
(Family-*Mimosaceae*)

It is probably a native of tropical America; naturalized more or less throughout India. Aqueous extract from dried leaves are employed to alleviate depression in Mexico. The extract (6 mg/kg and 8 mg/kg, i.p.) reduced immobility in the forced swimming test, thus showed antidepressant-like effect in rats[50].

Ocimum sanctum **Linn.**
(Family-*Lamiaceae*)

The plant known as *Tulsi* and Sacred or Holy basil is a herbaceous, much branched annual plant found throughout India. It helps in relieving the anxiety and agitation associated with depression[51, 52]. *Tulsi* also showed anti-aggressive and calming effect[53, 54]. Ethanolic extract of the leaves lowered the immobility in a behavioural despair involving forced swimming in rats and mice. This action was blocked by Haloperidol and Sulpiride, indicating a possible action involving dopaminergic neurons[55]. Methanol extract from roots (400 mg/kg, i.p.) showed increase in the swimming time, suggesting its antidepressant activity[56].

Withania somnifera **(Linn.) Dunal**
(Family-*Solanaceae*)

The drug consists of dried roots of the plant, widely distributed in North-western India. In the Indian traditional system of medicine, it is widely regarded as the Indian Ginseng. It is classified in Ayurveda, as a rasayana, a group of plant-derived drugs reputed to promote physical and mental health, augment resistance of the body against disease and diverse adverse environmental factors, revitalize the body in debilitated conditions and increase longevity. Standardized extract of roots (25 and 50 mg/kg, p.o.), significantly attenuated chronic stress induced mental depression, immunosuppression, cognitive deficit, male sexual dysfunction, hyperglycaemia, glucose intolerance, increase in plasma corticosterone levels and gastric ulceration in rats. Thus, it indicates significant antistress adaptogenic activity of the plant[57, 58]. A dose of (100 mg/kg, p.o.) produced a significant reduction in immobility period in a mouse model of chronic fatigue syndrome, in which mice were forced to swim for 6 minutes session on each day for 15 days and the immobility period was recorded. Co-administration of antioxidants and ***W. somnifera*** significantly reduced lipid peroxidation and restored the glutathione levels decreased by chronic swimming in mice[59]. Bioactive glycowithanolides (20 and 50 mg/kg, p.o.), isolated from roots, administered once daily for 5 days exhibited antidepressant effect, comparable with that induced by Imipramine (10 mg/kg,

i.p.), in the forced-swimming induced behaviour despair and learned helplessness tests[60].

***Piper methysticum* Forst**
(Family-*Piperaceae*)

In the South-Pacific islands, an aqueous extract of the roots of this plant, commonly known as Kava-Kava is consumed as a ritual stimulant; large doses cause intoxication. The standardized extract of kava-kava roots are used for the therapy of anxiety, tension, insomnia and restlessness. Kava pyrones, the major constituents of kava-kava, are generally considered to be responsible for the pharmacological activity in humans and animals. The inhibition of MAO-B by kava pyrones-enriched extract might be an important mechanism for their psychotropic activity[61, 62]. Relaxing and euphoric actions of the extract may be caused by the activation of the mesolimbic dopaminergic neurons[63].

Piper methysticum

***Siphocampylus verticillatus* (Cham.) G. Don**
(Family-*Campanulaceae*)

It is a native species that grows abundantly in the south of Brazil. Hydro-alcoholic extract (100-1000 mg/kg, i.p.) elicited a significant antidepressant effect, when assessed in the tail-suspension test and forced swimming test in mice. This antidepressant effect is most likely to be mediated through an interaction with adrenergic, dopaminergic, glutamatergic and serotonergic systems. The active principle(s) responsible are so far, not known, but much of the extract action could be related to the presence of the alkaloid, *cis*-8,10-di-n-propyllobelidiol hydrochloride dihydrate. Also other constituents like flavonoids (3-methoxy luteolin), triterpenes (α-amirin and β-amirin), and steroids (campesterol, β-sitosterol, stigmasterol and stigmasterol glycoside) could also be responsible, at least in part, for the antidepressant properties[64].

***Rhazya stricta* Decne**
(Family-*Apocynaceae*)

It is a shrub plant which grows commonly in the Arabian Peninsula, Sind, Baluchistan and Afghanistan. Aqueous extract of leaves of this plant showed antidepressant-like activity in forced-swimming test in rats and this might be due to its property of inhibiting both MAO-A and MAO-B. Anti depressant-like activity of the plant extract might be due to any of the constituents present, such as alkaloids with β-carboline nucleus (akuammidine, rhaziminine and tetrahydro secamine), flavonoids, namely isorhamnetine, 3- (6-dirhamnosyl galactoside)-7-rhamnoside and 3-(6-rhamnosyl galactoside)-7-rhamnoside[65].

***Apocynum venetum* Linn.**
(Family-*Apocynaceae*)

A wild shrub widely distributed in mid and Northwestern China. An extract of leaves significantly reduced immobility time in the forced swimming test after acute administration at a dosage of 125 mg/kg, an effect which was comparable to that of synthetic antidepressant Imipramine at a dosage of 20 mg/kg. The antidepressant effect of the plant might be due to hyperoside and isoquercitrin, which are major flavonoids in the extract[66].

***Morinda officinalis* F.C. How**
(Family-*Rubiaceae*)

It grows in humid areas of South-East China. The ethanolic extract showed antidepressant-like effect in animal models of depression such as forced-swimming test and learned helplessness paradigm. The antidepressant effect of the extract could at least partly be due to increase in serotonin levels at the neuron level[67, 68].

Morinda officinalis

Perilla frutescens

***Perilla frutescens* (Linn.) Britton** (Family-*Lamiaceae*)

The leaves of ***P. frutescens*** var. ***acuta* Kudo** (*Perillae Herba*) are found in some traditional oriental herbal medicines that are primarily used to treat disorders such as depression and anxiety. An oral administration of aqueous extract of the drug significantly reduced the duration of immobility in animal models of depression. Moreover, its 50% methanol extract of the aqueous extract and its 30% methanol extract also reduced the duration of immobility. The extract with anti-immobility effects was found to contain abundant rosmarinic acid. The oral and intraperitoneal administration of rosmarinic acid significantly reduced the duration of immobility. The result suggested that rosmarinic acid may be the main component involved in the antidepressive effect of *Perillae Herba* in the forced swimming test[69].

Rhizoma acori tatarinowii

The water decoction of ***Rhizoma acori tatarinowii***, a Chinese herb, significantly reduced the immobility times in rat forced swimming test and mouse tail suspension test, thus having antidepressant-like effect[70].

Antidepressant polyherbal formulations

Some polyherbal formulations prescribed by medical practitioners are: *Chaihu-Shugan-San*, *EuMil*, *Mentat*, Siotone, *Catuama*, *Banxia-houpu*, *Kami-shoyo-san* and *Sho-ju-sen*. It has been observed that the main ingredients of these preparations include: ***Withania somnifera*, *Ocimum sanctum*, *Asparagus racemosus* Willd.**, ***Emblica officinalis* Gaertn.**, ***Panax ginseng, Bacopa monnieri, Centella asiatica*, *Nardostachys jatamansi* DC.**, ***Evolvulus alsinoides* Linn.**, ***Valeriana jatamansi* Jones**, ***Acorus calamus* Linn.**, ***Tinospora cordifolia* (Willd.) Miers. ex Hook. f. & Thoms.**, ***Celastrus paniculatus* Willd.**, ***Saussurea lappa* C.B. Clarke**, ***Terminalia chebula* Retz.**, ***Terminalia bellirica* Roxb.**, ***Sasa kurinensis* Makino et Sibata**, ***Pinus densiflora* Sieb. et Zucc.** and ***Tribulus terrestris* Linn.**[71-81].

Conclusion

As mentioned above, there are a number of medicinal plants and formulations that possess antidepressant activity comparable to clinically effective synthetic antidepressants. Thus, plant based formulations can be effectively used for the treatment of mild to moderate cases of depression, with fewer side effects than the older synthetic agents. However, except for ***Hypericum perforatum***, more detailed clinical studies are required for the plants showing antidepressant activity in animal studies, so that depression can be treated effectively by use of plant-based formulations.

References

1. Rang HP, Dale MM and Ritter JM, Pharmacology, 4th edn, Churchill Livingstone, Edinburgh, 2000, pp. 550.
2. Gold PW, Goodwin FK and Chrousus GP, Clinical and biochemical manifestations of depression in relation to the neurobiology of stress: Part 1, *N Engl J Med*, 1988, **319**, 348-353.
3. Goodwin FK and Bunney WE, Depressions following reserpine: A re-evaluation, *Sem Psychiatry*, 1971, **3**, 435-448.
4. Madhu SM, Epidemiological study of prevalence of mental disorders in India, *Indian J Community Med*, 2001, **26**(4), 198-200.
5. Kessler RC, Epidemiology of women and depression, *J Affect Disord*, 2003, **74**(1), 5-13.
6. Fountoulakis KN, O'Hara R, Iacovides A, Camilleri CP, Kaprinis S, Kaprinis G and Yesavage J, Unipolar late-onset depression: A comprehensive review, *Ann Gen Hosp Psychiatry*, 2003, **2**(1), 11.
7. Nair MK, Paul MK and John R, Prevalence of depression among adolescents, *Indian J Pediatr*, 2004, **71**(6), 523-524.
8. Upton R, St. John's wort monograph, American Herbal Pharmacopoeia, Santa Cruz, CA, USA, 1997, pp.4.
9. Bombardelli E and Morazzoni P, *Hypericum perforatum*, *Fitoterapia*, 1995, **66**, 43.
10. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W and Melchart D, St. John's wort for depression – an overview and meta-analysis of randomized clinical trials, *Br Med J*, 1996, **313**, 253.
11. Kumar V, Singh PN, Jaiswal AK and Bhattacharya SK, Antidepressant activity of Indian *Hypericum perforatum* Linn. in rodents, *Indian J Exp Biol*, 1999, **37**, 1171-1176.
12. De Vry J, Maurel S, Schreiber RR de Beun and Jentzsch KR, Comparison of Hypericum extracts with imipramine and fluoxetine in animal models of depression and alcoholism,

Eur Neuropsychopharmacol, 1999, **9**, 461-468.

13. Tripathi YB and Pandey E, Role of alcoholic extract of shoot of *Hypericum perforatum* Linn. on lipid peroxidation and various species of free radicals in rats, *Indian J Exp Biol*, 2000, **37**, 567.

14. Hunt EJ, Lester CE, Lester EA and Treckett RL, Effect of St. John's wort on free radical production, *Life Sci*, 2001, **69**(2), 181-190.

15. Khalifa AE, *Hypericum perforatum* as a nootropic drug: enhancement of retrieval memory of a passive avoidance conditioning paradigm in mice, *J Ethnopharmacol*, 2001, **76**, 49-57.

16. Gastpar M, Singer A and Zeller K, Efficacy and tolerability of *Hypericum* extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline, *Pharmacopsychiatry*, 2005, **38**(2), 78-86.

17. Bjerkenstedt L, Edman GV, Alken RG and Mannel M, Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients, *Eur Arch Psychiatry Clin Neurosci*, 2005, **255**(1), 40-47.

18. Linde K and Knuppel L, Large-scale observational studies of hypericum extracts in patients with depressive disorders — a systematic review, *Phytomedicine*, 2005, **12**(1-2), 148-157.

19. Shelton RC, Keller MB, Gelenberg A, Dunner DL,Hirschfeld R, Thase ME, Russell J, Lydiard RB, Cristoph. PC, Gllop R, Todd L, Hellerstein D, Goodnick P, Keitner G, Stahl SM and Halbreich U, Effectiveness of St. John's wort in major depression: A randomized controlled trial, *JAMA*, 2001, **285**, 1978-1985.

20. Sanchez-Mateo CC, Prado B and Rabanal RM, Antidepressant effect of the methanol extract of several *Hypericum* species from Canary Islands, *J Ethnopharmacol*, 2002, **79**, 119-127.

21. Sanchez-Mateo CC, Bonkanka CX, Prado B and Rabanal RM, Antidepressant properties of some *Hypericum canariense* L. and *Hypericum glandulosum* Ait. extracts in the forced swimming test in mice, *J Ethnopharmacol*, 2005, **97**(3), 541-547.

22. ESCOP Monograph St. John's wort, European Scientific cooperative for phytomedicines. The Netherlands, Meppel, 1996.

23. Bystrov NS, Chernov BK, Dobrynin VN and Kolosov MN, The structure of hyperforin, *Tetrahedran Lett*, 1975, **32**, 2791.

24. Dorosseiv I, Determination of flavonoids in *Hypericum perforatum*, *Pharmazie*, 1985, 585.

25. Nielsen H and Arends P, Structure of the xanthone lignoid kielcorin, *Phytochemistry*, 1978, **17**, 2040.

26. Sparenberg B, Demisch L and Holzl J, Investigations of the antidepressive effects of St. John's wort, *Pharm Ztg Wiss*, 1993, **6**, 50.

27. Muller WE, Singer A, Wonnermann M, Hafner U, Rolli M and Schafer C, Hyperforin represents the neurotransmitter reuptake inhibiting constituent of *Hypericum* extract, *Pharmacopsychiatry*, 1998, **31**, 16.

28. Chatterjee SS, Bhattacharya SK, Wonnermann M, Singer A and Muller WE, Hyperforin as a possible antidepressant component of *Hypericum* extract, *Life Sci*, 1998, **63**, 499-510.

29. Barnes J, Anderson LA and Phillipson JD, St. John's wort (*H. perforatum* L): a review of its chemistry, pharmacology and clinical properties, *J Pharm Pharmacol*, 2001, **53**, 583-600.

30. Singer A, Wonnermann M and Muller WE, Hyperforin, a major antidepressant constituent of St. John's wort, inhibits serotonin uptake by elevating free intracellular Na^+, *J Pharmacol Exp Ther*, 1999, **290**, 1363-1368.

31. Calapai G, Crupi A, Firenzuoli F, Inferrera G, Squadrito F, Parisi A, De Sarro G and Caputi A, Serotonin, norepinephrine and dopamine involvement in the antidepressant action of *Hypericum perforatum*, *Pharmacopsychiatry*, 2001, **34**(2), 45-49.

32. Yu PH, Effect of the *Hypericum perforatum* on serotonin turnover in the mouse brain, *Pharmacopsychiatry*, 2000, **33**(2), 60-65.

33. Muller WE, Rolli M, Schafer C and Hafner U, Effects of Hypericum extract (LI 160) in biochemical models of antidepressant activity, *Pharmacopsychiatry*, 1997, **30**(2), 102-107.

34. Muller WE, Singer A and Wonnemann M, Mechanism of action of St. John's wort extract, *Schweiz Rundsch Med Prax*, 2000, **89**(50), 2111-2121.

35. Dar A and Khatoon S, 1997a, Antidepressant activities of *Areca catechu* fruit extract, *Phytomedicine*, 1997, **4**, 41-45.

36. Dar A and Khatoon S, 1997b, Antidepressant effects of ethanol extract of *Areca catechu* in rodents, *Phytother Res*, 1997, **11**, 174-176.

37. Dar A and Khatoon S, Behavioral and biochemical studies of dichromethane fraction from the *Areca catechu* Nut, *Pharmacol Biochem Behav*, 2000, **65**, 1-6.

38. Sairam K, Dorababu M, Goel RK and Bhattacharya SK, Antidepressant activity of standard extract of *Bacopa monniera* in experimental models of depression in rats, *Phytomedicine*, 2002, **9**(3), 207-211.

39. Chen Y, Han T, Qin L, Rui Y and Zheng H, Effects of total triterpenes from *Centella*

asiatica on the depression behavior and concentration of amino acid in forced swimming mice, *Zhong Yao Cai*, 2003, **26**(12), 870-873.

40. Winterhoff H, Spengler B, Christoffel V, Butterweck V and Lohning A, *Cimicifuga* extract BNO 1055: reduction of hot flushes and hints on antidepressant activity, *Maturitas*, 2003, **44** (Suppl 1), S51-S58.

41. Jain NN, Ohal CC, Shroff SK, Bhutada RH, Somani RS, Kasture VS and Kasture SB, *Clitoria ternatea* and the CNS, *Pharmacol Biochem Behav*, 2003, **75**(3), 529-536.

42. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi AH and Khalighi-Cigaroudi F, Comparison of *Crocus sativus* Linn. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial, *MC Complement Altern Med*, 2004, **4**(1), 12.

43. Noorbala AA, Akhondzadeh S, Tahmacebi-Pour N and Jamshidi AH, Hydro-alcoholic extract of *Crocus sativus* L, versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial, *J Ethnopharmacol*, 2005, **97**(2), 281-284.

44. Yu ZF, Kong LD and Chen Y, Antidepressant activity of aqueous extracts of *Curcuma longa* in mice, *J Ethnopharmacol*, 2002, **83**(1-2), 161-165.

45. Kaur G and Kulkarni SK, Reversal of forced swimming-induced chronic fatigue in mice by antidepressant and herbal psychotropic drugs, *Indian Drugs*, 1998, **35**(12), 771-777.

46. Shah ZA, Sharma P and Vohora SB, Ginkgo biloba normalises stress-elevated alterations in brain catecholamines, serotonin and plasma corticosterone levels, *Eur Neuropsychopharmacol*, 2003, **13**(5), 321-325.

47. Trick L, Boyle J and Hindmarch I, The effects of *Ginkgo biloba* extract (LI 1370) supplementation and discontinuation on activities of daily living and mood in free living older volunteers, *Phytother Res*, 2004, **18**(7), 531-537.

48. Qin XS, Jin KH, Ding BK, Xie SF and Ma H, Effects of extract of *Ginkgo biloba* with venlafaxine on brain injury in a rat model of depression, *Chin Med J (Engl)*, 2005, **118**(5), 391-397.

49. Nakazawa T, Yasuda T and Ohsawa K, Metabolites of orally administered *Magnolia officinalis* extract in rats and man and its antidepressant-like effects in mice, *J Pharm Pharmacol*, 2003, **55**(11), 1583-1591.

50. Molina M, Contreras CM and Tellez-Alcantara P, *Mimosa pudica* may possess antidepressant actions in the rat, *Phytomedicine*, 1999, **6**(5), 319-323.

51. Dixit KS, Srivastva M, Srivastva AK, Singh SP and Singh N, Effect of *Ocimum sanctum* on stress induced alterations upon some brain neurotransmitters and enzyme activity, *Proc XVIIIth Annual Conference of Indian Pharmacological Society*, JIPMER, Pondicherry, 1985, pp.57.

52. Singh N, Misra N, Srivastva AK, Dixit KS and Gupta GP, Effects of anti-stress plants on biochemical changes during stress reaction, *Indian J Pharmacol*, 1991, **23**(3), 137-142.

53. Singh N, A pharmaco-clinical evaluation of some Ayurvedic crude plant drugs as anti-stress agents and their usefulness in some stress diseases of man, *Ann Nat Acad Ind Med*, 1986, **2**(1), 14-26.

54. Singh N and Misra N, Experimental methods – Tools for assessment of anti-stress activity in medicinal plants, *J Biol Chem Res*, 1993, **12** (182), 124-127.

55. Sakina MR, Dandiya PC, Hamdard ME and Hameed A, Preliminary psychopharmacological evaluation of *Ocimum sanctum* leaf extract, *J Ethnopharmacol*, 1990, **28**(2), 143-150.

56. Maity TK, Mandal SC, Saha BP and Pal M, Effects of *Ocimum sanctum* roots extract on swimming performance in mice, *Phytother Res*, 2000, **14**(2), 120-121.

57. Singh N, Singh SP, Sinha JN, Shanker K and Kohli RP, *Withania somnifera* (Ashwagandha): A rejuvenator herbal drug which enhances survival during stress (An adpatogen), *Int J Crude Drug Res,* USA, 1982, **3**, 29-35.

58. Bhattacharya SK and Muruganandam AV, Adaptogenic activity of *Withania somnifera*: an experimental study using a rat model of chronic stress, *Pharmacol Biochem Behav*, 2003, **75**(3), 547-555.

59. Singh A, Naidu PS, Gupta S and Kulkarni SK, Effects of natural and synthetic antioxidants in a mouse model of chronic fatigue syndrome, *J Med Food*, 2002, **5**(4), 211-220.

60. Bhattacharya SK, Bhattacharya A, Siaram K and Ghoshal S, Anxiolytic-antidepressant activity of *Withania somnifera* glycowithanolides: an experimental study, *Phytomedicine*, 2000, **7**(6), 463-469.

61. Uebelhack R, Franke L and Schewe HJ, Inhibition of MAO-B by kavapyrone-enriched extract from *Piper methysticum* Foster (kava-kava), *Pharmacopsychiatry*, 1998, **31**(5), 187-192.

62. Wheatley D, Kava and Valerian in the treatment of stress-induced insomnia, *Phytother Res*, 2001, **15**(6), 549-551.

63. Baum SS, Hill R and Rommelspacher H, Effect of kava extract and individual kava pyrones on neurotransmitter levels in the nucleus accumbens of rats, *Prog Neuropsychopharmacol Biol Psychiatry*, 1998, **22**(7), 1105-1120.

64. Rodrigues AL, da Silva GL, Mateussi AS, Fernandes ES, Miguel OG, Yunes RA, Calixto JB and Santos ARS, Involvement of monoaminergic system in the antidepressant-like effect of the hydroalcoholic extract of *Siphocampylus verticillatus*, *Life Sci*, 2002, **70**, 1347-1358.

65. Ali BH, Bashir AK and Tanira MO, The effect of *Rhazya stricta* Decne, A traditional medicinal plant, on the forced swimming test in rats, *Pharmacol Biochem Behav*, 1998, **59**(2), 547-550.

66. Butterweck V, Nisshibe S, Sasaki T and Uchida M, Antidepressants effects of *Apocynum venetum* leaves in the forced swimming test, *Biol Pharm Bull*, 2001, **24**(7), 848-851.

67. Zhang ZQ, Yuan L, Zhao N, Xu YK, Yang M and Luo ZP, Antidepressant effect of the ethanolic extracts of the roots of *Morinda officinalis* in rats and mice, *Chin Pharm J*, 2000, **35**, 739-741.

68. Zhang ZQ, Huang SJ, Yuan L, Zhao N, Xu YK, Yang M, Luo ZP, Zhao YM and Zhang YX, Effect of *Morinda officinalis* oligosaccharides on performance of the swimming tests in mice and rats and the learned helplessness paradigm in rats, *Chin J Pharmacol Toxicol*, 2001, **15**, 262-265.

69. Takeda H, Tsuji M, Matsumiya T and Kudo M, Identification of rosmarinic acid as a novel antidepressive substance in the leaves of *Perilla frutescens* Britton var. *acuta* Kudo (*Perillae Herba*), *Nihon Shinkei Seishin Yakurigaku Zasshi*, 2002, **22**(1), 15-22.

70. Li M and Chen H, Antidepressant effect of water decoction of *Rhizoma acori* tatarinowii in the behavioral despair animal models of depression, *Zhong Yao Cai*, 2001, **24**(1), 40-41.

71. Kim SH, Han J, Seog DH, Chung JY, Kim N, Hong Park Y and Lee SK, Antidepressant effect of Chaihu-Shugan-San extract and its constituents in rat models of depression, *Life Sci*, 2005, **76**(11), 1297-1306.

72. Bhattacharya A, Muruganandam AV, Kumar V and Bhattacharya SK, Effects of polyherbal formulation, EuMil, on neurochemical perturbations induced by chronic stress, *Indian J Exp Biol*, 2002, **40**(10), 1161-1163.

73. Muruganandam AV, Kumar V and Bhattacharya SK, Effect of polyherbal formulation, EuMil, on chronic stress-induced homeostatic perturbations in rats, *Indian J Exp Biol*, 2002, **40**(10), 1151-1160.

74. Verma A and Kulkarni SK, Effect of a herbal psychotropic preparation, BR-16A (Mentat), on performance of mice on elevated plus-maze, *Indian J Exp Biol*, 1991, **29**, 1120-1123.

75. Bhatacharya SK, Nootropic effect of BR-16A (Mentat®), a psychotropic herbal formulation, on cognitive deficits induced by prenatal undernutrition, postnatal environment impoverishment and hypoxia in rats, *Indian J Exp Biol*, 1994, **32**, 31-36.

76. Bhattacharya SK, Bhattacharya A and Chakrabarti A, Adaptogenic activity of Siotone, a poly herbal formulation of Ayurvedic rasayanas, *Indian J Exp Biol*, 2000, **38**(2), 1119-1128.

77. Campos MM, Fernandes ES, Ferreira J, Bortolanza LB, Santos AR and Calixto JB, Pharmacological and neurochemical evidence for antidepressant-like effects of the herbal product Catuama, *Pharmacol Biochem Behav*, 2004, **78**(4), 757-764.

78. Wang YM, Kong LD and Huang ZQ, Screening of antidepressant fractions of *Banxia-houpu* decoction, *Zhongguo Zhong Yao Za Zhi*, 2002, **27**(12), 932-936.

79. Guo Y, Kong L, Wang Y and Huang Z, Antidepressant evaluation of polysaccharides from a Chinese herbal medicine *Banxia-houpu* decoction, *Phytother Res*, 2004, **18**(3), 204-207.

80. Masuda Y, Ohnuma S, Sugawara J, Kawarada Y and Sugiyama T, Behavioral effect of herbal glycoside in the forced swimming test, *Methods Find Exp Clin Pharmacol*, 2002, **24**(1), 19-21.

81. Kuribara H, Tomioka H, Takhashi R, Onozato K, Murohashi N, Numajiri T, Iwata H and Koya S, An antidepressant effect of *Sho-ju-sen*, a Japanese herbal medicine, assessed by learned helplessness model in mice, *Phytother Res*, 2004, **18**(2), 173-176.