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. Patients with depression have symptoms that reflect decrease in brain monoamine neurotransmitters, specifically norepinephrine, serotonin and dopamine. 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.

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. 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. The prevalence of major depression is estimated to be 2% in the general population over 65 years of age. About 11.2% school dropouts had severe to extreme grades of depression as against 3% among school going and nil among college going adolescents.

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.

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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Medicinal plants as antidepressants


It is better known as St. John’s wort, has been used clinically for centuries. 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. 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. 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. *Hypericum* extract, standardized to both hypericin and hyperforin, appears to have significant free radical scavenging properties in cell-free and human vascular systems. These favourable effects were achieved with *H. perforatum* having the ability to treat both depression and amnesia with lower potential side effects. *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. Efficacy and tolerability of *Hypericum* LI 160 was comparable to fluoxetine in mild to moderate depression in a 4-week randomized, double-blind trial. Thus, *Hypericum* extract can be effective in routine treatment of mild to moderate depressive disorders. However, it was not effective for treatment of patients with major depression.

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. *Hypericum* contains numerous compounds with documented biological activity. Constituents that have stimulated the most interest include the naphthodianthrones namely hypericin and...
pseudohypericin\textsuperscript{22}; phloroglucinols\textsuperscript{23} namely hyperforin and adhyperforin; flavonoids\textsuperscript{24} like flavonol glycosides, viz. rutin, queratin, isoqueratin, hyperin/ hyperoside and aglycones, viz. kaempferol, luteolin, myricetin and quercetin; xanthones namely kielkorin in roots\textsuperscript{25}, 1,3,6,7-tetrahydroxyxanthone in trace amounts in leaves and stems\textsuperscript{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 \textit{H. perforatum}\textsuperscript{27-29} and this may be involved in inhibition of uptake of serotonin, noradrenaline and dopamine\textsuperscript{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\textsuperscript{32}. LI 160, standardized extract of \textit{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\textsuperscript{33, 34}.

\textit{Areca catechu} Linn.
\textit{(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\textsuperscript{35, 36}. Alkaldoids 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\textsuperscript{37}.

\textit{Bacopa monnieri} (Linn.) Penn.
\textit{(Family-Scrophulariaceae)}

It is commonly known as \textit{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, bacosite 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\textsuperscript{38}.

\textit{Centella asiatica} (Linn.) Urban
\textit{(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\textsuperscript{39}.

\textit{Cimicifuga racemosa} (Linn.) Nutt.
\textit{(Family-Ranunculaceae)}

It is distributed in temperate Himalayas from Kashmir to Bhutan (2300-4000 m), Eastern Europe and Siberia. Ethanolic-aqueous extracts of \textit{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\textsuperscript{40}.

\textit{Clitoria ternatea} Linn.
\textit{(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\textsuperscript{41}.

\textit{Crocus sativus} Linn.
\textit{(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\textsuperscript{42, 43}.

\textit{Curcuma longa} Linn.
\textit{(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-dependent 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\(^4^4\).

**Evening Primrose oil**

Evening Primrose 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 Primrose 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\(^4^5\).

**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\(^4^6\). The extract has a demonstrable effect in improving mood in healthy older volunteers\(^4^7\). 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\(^4^8\).

**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\(^4^9\).

**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\(^5^0\).

**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\(^5^1,5^2\). *Tulsi* also showed anti-aggressive and calming effect\(^5^3,5^4\). 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\(^5^5\). Methanol extract from roots (400 mg/kg, i.p.) showed increase in the swimming time, suggesting its antidepressant activity\(^5^6\).

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

The drug consists of dried roots of the plant, widely distributed in Northwestern 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\(^5^7,5^8\). 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\(^5^9\). 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\(^6\).

**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\(^63\).

**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\(^67, 68\).
**Review Article**

**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.ENV

**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.

**Antidepressant polyherbal formulations**


**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.

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