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Anti-depression potential of herbal drugs: An overview

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ABSTRACT

India is sitting on a gold mine of well-recorded and traditionally well practiced knowledge of herbal medicine. There are very few medicinal herbs of commercial importance, which are not found in this country. India officially recognizes over 3000 plants for their medicinal value. It is generally estimated that over 6000 plants in India are in use in traditional, folk and herbal medicine. There are about 9000 firms manufacturing traditional Ayurvedic medicines in India. Major Pharmaceutical companies are currently conducting extensive research on plant materials for their potential medicinal value. Depression is a common mood disorder that impacts on all aspect of a person's life, involving mood, thoughts, thinking, behavior, feelings etc. It is a potentially life-threatening disorder that affects hundreds of millions of people all over the world. It can occur at any age from childhood to late life. According to the World Health Organization, depression is a mental health problem affecting an estimated 121 million people worldwide. Objective of the present review is to explore some of the medicinal plant and their phytoconstituents for their anti-depressant like activity.

Key words:- Bipolar, Depression, Plants, SSRI's, Unipolar.

INTRODUCTION

Depression is one of the major public health care issue all over the world. According to WHO estimation, 121 million people world wide suffer from clinical depression. The high prevalence of suicide in depressed patients (up to 15%) and other complications arising from stress and its effects on the cardiovascular system have suggested that it will be the second leading cause of death by the year 2020 [1]. 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 [2]. Depression is the leading cause of disease related disability among women in the world today. It is much more common among women's then in man with female/male risk ratio roughly 2:1 [3].

Classification of depression is based on the mono and bipolar dichotomy, which separates those patients with depressive symptoms only from those that fluctuate between depression and mania or have only manic symptoms. The unipolar depression (in which mood swings are always in the same direction) is of two types reactive and endogenous. Bipolar depression, which usually appears in early adult life, is less common and results in oscillating depression and mania over a period of few weeks [4, 5].

Treatment of depressant includes the use of following category of drugs:-

- 1) Tricyclic antidepressants (TCAs)
- 2) Tetracyclic antidepressants
- 3) Selective serotonin re-uptake inhibitors (SSRIs)
- 4) Serotonin and norepinephrine re-uptake inhibitors (SNRIs)
- 5) Serotonin receptor modulators (SRMs)
- 6) Monoamine oxidase inhibitors (MAOIs)
- 7) Lithium Salts

But these drugs are associated with certain side effects which are as follows:-

- 1) Tricyclic & tetracyclic antidepressants: Dizziness, headache, sweating, tremor, palpitation, dry mouth, constipation, blurred vision, difficulty passing urine, and orthostatic hypotension. Other less-common adverse effects include seizure, liver dysfunction, ECG changes and abnormal blood count.
- 2) SSRIs: Nausea, vomiting, gastrointestinal discomfort, dry mouth, tremor, headache, sweating, sexual dysfunction and weight loss, etc. Occasionally, some patients may experience excitement, anxiety, insomnia, restlessness or seizure.
- 3) SNRIs: Similar to SSRIs. But it may also cause hypertension at high dose.
- 4) SRMs: Tremor, headache, constipation, weight gain and hypotension. Some patients may develop seizure, abnormal liver function tests and blood disorder, etc.
- 5) MAOIs: Dizziness, headache, nervousness, gastrointestinal disturbance, etc. It may also interact with tyramine rich food or drinks, as a consequence inducing sweating, vomiting and hypertensive crisis. e.g. pigeon, alcoholic beverages, cheese, chicken and beef liver, chocolate or cheese, etc.
- 6) Lithium salts: Bitter taste, dry mouth, tremor, polyuria, fatigue and weight gain. Other less-common side effects include hyperthyroidism, hypothyroidism, ECG changes, raised anti-diuretic hormone concentrations, renal failure or leucocytosis.

Along with these side effects the cost of these drugs is very high, and also it will take almost a decade to develop a new drug. On the other hand plant based drugs have long history of use and better patient tolerance as well as public acceptance. They are easily available at low cost as compare with modern drugs. Also phytoconstituents isolated from them may act as a lead compound for new pharmaceuticals.

Medicinal plants have always played a vital role as remedies in the treatment of human ailments. Large numbers of medicinal plants are in use in the traditional Ayurvedic and Unani system of medicine in India [6, 7]. The World Health Organization (WHO) has estimated that 80% of the earth's (6 billion) inhabitants rely upon traditional medicine for their primary health care needs and major part of this therapy involves the use of plant extracts or their active principles [8].

In today's world, 30% of the Pharmaceutical preparations are manufactured from plants. Various parts of the plants such as roots, stems, bark, gum, leaves, fruits, seeds and flowers are used for medicinal purposes. It is noted that the same plants are used in a number of different ways [9].

Most of the people believe that modern medicines are not really helpful in treating certain diseases such as, Depression, Arthritis, Leprosy, Psoriasis etc. These diseases are not well treatable by any known medical system except our old-age plant based traditional medicines. In many developing countries, Phyto-pharmaceuticals are the main pillar of national health care programme.

Plants reported to possess antidepressant-like activity

Following plants have been reported to have antidepressant-like activity:

Aloysia polystachya

Hydro-alcoholic extract of the leaves of *Aloysia polystachya* (Griseb.) Moldenke (Family: Verbenaceae) at the dose of 12.5, 25 and 50 mg/kg, *i.p.* produced antidepressant like action in female Sprague-Dawley rats when tested in Forced Swim Test (FST). Thujone and carvone was the main Phytoconstituent responsible for antidepressant-like action. The efficacy of the extract was comparable to fluoxetine (10 mg/kg, *i.p.*) and imipramine (12.5 mg/kg, *i.p.*). [10]

Anemarrhena asphodeloides

Sarsasapogenin like phytoconstituent isolated from the leaves of *Anemarrhena asphodeloides* Bunge (Family: Liliaceae) showed significant anti-depressant like activity in mice at the dose of 12.5, 25 and 50 mg/kg, *p.o.* for 14 consecutive days. Sarsasapogenin (50 mg/kg) markedly increased NE and 5-HT levels in hypothalamus and hippocampus. [11]

Aniba riparia

Aniba riparia (Nees) Mez (Family: Lauraceae) showed its anti-depressant like activity due the its Phytoconstituent riparin III; which at the dose of 25 and 50 mg/kg, *i.p.*, showed antidepressant-like activity in mice when tested in Tail Suspension Test (TST) and FST.[12]

Apocynum venetum

Extract of the leaves of *Apocynum venetum* L. (Family: Apocynaceae) contains flavonoids hyperoside and isoquercitrin which shows significant antidepressant-like action in male rats. This may be due to interaction with adrenergic and dopaminergic system. [13, 14]

Areca catechu

Ethanol extract [15, 16] and dichloromethane fraction [17] of the fruits of *Areca catechu* (Family: Arecaceae) showed significant antidepressant-like activity in rats and mice when tested in FST and TST.

Bacopa monniera

Methanolic extract of *Bacopa monniera* Wettst. (syn. *Herpestis monniera* L.; Family: Scrophulariaceae) at the dose of 20 and 40 mg/kg orally for 5 days to Charles-Foster albino rats (either sex), significantly showed antidepressant-like effect in FST and learned helplessness models; which is comparable to imipramine administered at a dose of 15 mg/kg *i.p.* [18]

Camellia sinensis

The aqueous extract of the leaves of *Camellia sinensis* (L.) O. Kuntze (Family: Theaceae) at the dose of 100 mg/kg, showed significant antidepressant-like activity in normal, reserpinised (2 mg/kg, *i.p.*) and diabetic (streptozotocin-induced) male mice when tested in FST. [19]

Canavalia brasiliensis

The lectins isolated from the seeds of *Canavalia brasiliensis* (Family: Leguminosae) at the dose of 1–10 µg/site, *i.v.* significantly reduced immobility time of male Swiss albino mice in FST. [20]

Casimiroa edulis

The hydroalcoholic extract of the leaves of *Casimiroa edulis* (Family: Rutaceae) showed significant antidepressant-like activity in male and female rats subjected to FST without affecting locomotor activity. [21]

Cayratia japonica

Seven flavonoids compounds (apigenin-7-O-beta-D-glucuronopyranoside, apigenin, luteolin, luteolin-7-O-beta-D-glucopyranoside, taxifolin, aromadendrin and quercetin) isolated from the methanol extract of whole plants and fruits of *Cayratia japonica* (Thunb.) Gagnepain (Family: Vitaceae) significantly inhibited MAO. Out of these seven flavonoids Quercetin was found to be a potent MAO-A inhibitory effect while apigenin and luteolin preferentially inhibited MAO-A. [22]

Cecropia glazioui

Aqueous extract of *Cecropia glazioui* Sneth (Family: Cecropiaceae) and butanolic fractions significantly reduced the immobility of rats in FST. The butanolic fractions (Catechin and epicatechin) significantly increased hippocampal monoamines levels and inhibited the uptake of serotonin, dopamine and noradrenaline by synaptosomes of different brain regions. [23]

Centella asiatica

Total triterpenes isolated from *Centella asiatica* (Family: Apiaceae) showed antidepressant-like action in mice when tested in FST. The antidepressant effect may be due to decreased activity of hypothalamic-pituitary adrenal (HPA) axis and by increasing the levels of monoamine neurotransmitters. [24, 25]

Cimicifuga racemosa

The ethanolic (58% *v/v*) extract of *Cimicifuga racemosa* (Family: Ranunculaceae) administered at doses of 25, 50 mg/kg and 100 mg/kg to female mice showed significant antidepressant-like action in TST. [26]

Cissampelos sympodialis

At the dose of 20 and 40 mg/kg (*i.p.*) and 125, 250 and 500 mg/kg (*p.o.*); ethanolic extract of the leaves of *Cissampelos sympodialis* Eichl. (Family: Menispermaceae) showed significant antidepressant-like activity in male mice when tested in FST (characteristic of human depression) in rats. [27]

Clitoria ternatea

Clitoria ternatea Linn (Family: Fabaceae)'s methanolic extract (aerial part) at the dose of 100 and 400 mg/kg *p.o.* significantly reduced the immobility time of mice in TST; which is comparable to fluoxetine administered at a dose of 10 mg/kg *i.p.* [28]

Coleus forskohlii

Forskolin (diterpene) and NKH477 (water soluble derivative of forskolin) isolated from *Coleus forskohlii* (Family: Lamiaceae) at dose of 0.01- 1.0 mg/kg, *i.p.* decreased the immobility time of

rats subjected to FST. The antidepressant action of forskolin or NKH477 at the dose of 0.05mg/kg was 300 times more potent than that of 15 mg/kg amitriptyline. [29]

Convolvulus pluricaulis

The chloroform fraction of total ethanolic extract of *Convolvulus pluricaulis* Choisy (Family: Convolvulaceae) at the doses of 50 and 100 mg/kg for 10 successive days, significantly reduced the immobility period of male Swiss albino mice when tested in FST and TST. [30]

Curcuma longa

The aqueous extracts of *Curcuma longa* L. (Family: Zingiberaceae) administered at dose of 140 to 560 mg/kg for 14 days to male ICR mice elicited dose-dependant reduction of immobility time in TST and FST. [31]

Echium amoenum

Aqueous extract of dried flowers of *Echium amoenum* (Family: Boraginaceae) at the dose of 375 mg/day, for 6- weeks showed antidepressant-like effect in double blind, parallel-group trials of 35 patients. [32]

Epimedium brevicornum

Icariin, a major flavonoid isolated from *Epimedium brevicornum* Maxim (Family: Berberidaceae) at the doses of 17.5 and 35 mg/kg, orally for 21 and 7 consecutive days respectively to KunMing male mice shortened immobility time in FST and TST; which is comparable to fluoxetine (10 mg/kg) and amitriptyline (10 mg/kg). [33]

Gastrodia elata

The hydroalcoholic (75%) extract of *Gastrodia elata* (Family: Orchidaceae) roots administered orally at doses of 100, 200 and 300 mg/kg for 7 successive days to mice reduced the immobility time in FST and TST; which is comparable to fluoxetine at dose of 20 mg/kg. [34]

Gentiana kochiana

Diethylether extract of aerial parts of *Gentiana kochiana* (Family: Gentianaceae) at the dose of 20 mg/kg *s.c.* for 10 successive days significantly decreased immobility period of mice in FST. Gentiacaulein, the active component of the extract strongly inhibited rat microsomal MAO-A. [35]

***Gossypium herbaceum* (Cottonseeds)**

Aqueous extract of *Gossypium herbaceum* (Family: Malvaceae) showed significant antidepressant-like effect due to activation of adenylyl cyclase-cAMP pathway in signal transduction system and hence protecting the neurons from the lesion. [36]

Hippeastrum vittatum

Montanine (Isoquinoline alkaloid), isolated from bulbs of *Hippeastrum vittatum* Herbert (Family: Amaryllidaceae), at the dose of 3.0 mg/kg *i.p.* to Swiss albino mice showed significant antidepressant-like activity in FST. [37]

Humulus lupulus

Carbon di-oxide (CO₂) extract and its fraction (containing alpha-acids) of *Humulus lupulus* L. (Family: Cannabaceae), administered three times before the test to rats, produced significant antidepressant-like effect in behavioral despair test. [38]

Hypericum canariense

The methanol extract of the aerial parts of *Hypericum canariense* L. (Family: Clusiaceae) and butanol and chloroform fractions of methanol extract showed significant antidepressant-like activity in mice subjected to FST. [39, 40]

Hypericum caprifoliatum

Cyclohexane extract *Hypericum caprifoliatum* Cham & Schlecht (Family: Guttiferae) reduced the immobility period of rats and mice subjected to FST. *In vitro*, lipophilic extract and its main component (a phloroglucinol derivative) inhibited monoamine uptake in a concentration-dependent manner. [41, 42]

Hypericum reflexum

Butanol and chloroform fractions of the methanolic extract of aerial parts of *Hypericum reflexum* L. fil. (Family: Hypericaceae), at the dose of 500 mg/kg *p.o.*, significantly reduced the immobility time of Swiss albino mice in FST. [43]

Ilex pubescens

The petroleum extract of the stems of *Ilex pubescens* Hook. et Arn. (Family: Aquifoliaceae) decreased significantly the number of escape failures as compared to control in male ICR mice subjected to learned helplessness model, thus showed antidepressant-like activity. [44]

Inula japonica

Pure Phytoconstituent Japonicins (flavonols) isolated from alcoholic (70%) extract of *Inula japonica* (Family: Asteraceae) showed significant antidepressant-like activity. [45]

Japanese valerian Roots

Ethanol (30%) extract of Japanese valerian (Family: Valerianaceae) roots administered at the dose of 4.1 g/kg exhibited potent antidepressant-like activity in male rats subjected to FST. [46]

Kielmeyera coriacea

Total ethanol extract of the stem of *Kielmeyera coriacea* Mart. (Family: Clusiaceae), at the dose of 60 mg/kg to rats significantly reduced the immobility time in FST. The antidepressant-like action was mediated through serotonergic mechanism. [47] The dichloromethane fraction of the ethanol extract at the dose of 5 mg/kg for 45 successive days significantly reduced the immobility period in FST. [48]

Lavandula angustifolia

The tincture (1:5 in 50% alcohol) of the dried flowers of *Lavandula angustifolia* Mill. (Family: Lamiaceae) at the dose of 60 drops/day for 4 weeks showed significant antidepressant-like activity in 45 outpatients in doubleblind and single-center trials. [49]

Lepidium meyenii

Aqueous extract of hypocotyls of *Lepidium meyenii* Walp. (Family: Brassicaceae), at the dose of 1g/kg/day, *p.o.* to Swiss female ovariectomized mice for 21 consecutive days significantly showed anti-depressant like activity. [50]

Lobelia inflata

The methanolic extract of *Lobelia inflata* L. (Family: Campanulaceae) leaves reduced the duration of immobility of male mice subjected to FST. β -Amyrin palmitate was the phytoconstituent isolated responsible for anti-depressant action. [51]

Magnolia officinalis

The active phytoconstituent such as magnolol and dihydroxydihydromagnolol obtained from the aqueous extract of *Magnolia officinalis* (Family: Magnoliaceae) bark, at dose of 50-100 mg/kg, *i.p.* to mice, shows anti-depression like activity. [52]

Mimosa pudica

Aqueous extract (6 mg/kg and 8 mg/kg, *i.p.*) from dried leaves of *Mimosa pudica* (Family: Fabaceae) showed antidepressant-like effect by reducing the immobility period of rats subjected to FST. [53]

Mitragyna speciosa

Aqueous extract (100, 300 and 500 mg/kg *p.o.*) of leaves of *Mitragyna speciosa* Korth (Family: Rubiaceae) showed antidepressant like activity in male mice.[54] The extract containing approximately 60% mitragynine (a major indole alkaloid) which at the dose of 60 and 90 mg/kg, *i.p.* significantly reduced the immobility time of mice in FST. [55]

Morinda officinalis

The ethanol extract and oligosaccharides from *Morinda officinalis* How (Family: Rubiaceae) showed antidepressant activity in both mice and rats subjected to FST. [56, 57] The aqueous extract (50 mg/kg) of the roots showed antidepressant-like activity in male Kunming mice subjected to FST. [58]

Myristica fragrans

The *n*-hexane extract of *Myristica fragrans* (Family: Myristicaceae) seeds at the dose of 5, 10, and 20 mg/kg orally for 3 successive days to male mice significantly decreased immobility time in FST and TST without any significant effect on loco-motor activity. [59]

***Nelumbo nucifera* Gaertn (Nelumbinis Semen)**

Nelumbo nucifera Gaertn. (Family: Nymphaeaceae) shows antidepressant-like action in chronic mild stress model and FST. The anti-depressant potential is found to be greater than *Hypericum perforatum*. [60] It significantly increased 5-HT in normal conditions and reversed stress-induced decrease of 5-HT release in the hippocampus of rats subjected to chronic mild stress for 8 weeks. [61]

Ocimum sanctum

The ethanol extract of the leaves of *Ocimum sanctum* L. (Family: Labiateae), significantly decreased the immobility of rats and mice in FST. The antidepressant-like action was blocked by haloperidol and sulphiride, indicating the involvement of dopaminergic neurons. [62] The methanol extract of *O. sanctum* roots (400 mg/kg, *i.p.*) increased the mice swimming time and thus suggested its antidepressant-like action. [63]

Paullinia cupana

Guarana, an extract of the seeds of *Paullinia cupana* Mart. (Family: Sapindaceae), at the dose of 25 and 50 mg/kg, *p.o.* to mice, significantly decreased the immobility period in FST. [64]

Perilla frutescens

The leaves of *Perilla frutescens* Britton var. *acuta* Kudo (Family: Labiatae) are primarily used in affective disorders like depression and anxiety. The aqueous extract of *P. frutescens* and its 50% methanol fraction reduced the duration of immobility of mice subjected to FST. Rosmarinic acid, the active phytoconstituent of the extract, also significantly produced anti-immobility effect in

FST. Another phytoconstituent Apigenin from *P. frutescens* showed antidepressant-like activity in FST through dopaminergic mechanisms in the mouse brain. [65]

Piper longum

Piperine the phytoconstituent, isolated from ethanol extract of the fruits of *Piper longum* (Family: Piperaceae) significantly reduced the immobility time in TST. It also inhibited MAO-A and MAO-B, hence possessed an antidepressant potential. [66]

Plantago asiatica

The petroleum ether extract of *Plantago asiatica* L. (Family: Plantaginaceae) at the dose of 5 and 10 mg/kg, *p.o.* shows significant anti-depressant like activity in male mice. [44]

Polygala tenuifolia

The polygalatenosides A, B, C, D and E, obtained from the roots of *Polygala tenuifolia* (Family: Polygalaceae), has got anti-depressant potential. [67]

Psoralea corylifolia

Furocoumarins isolated from the seeds of *Psoralea corylifolia* L. (Family: Leguminosae) at the dose of 7.5 to 100 mg/kg, *p.o.* for 3 successive days significantly decreased the immobility time of male mice employing FST. The efficacy of the higher doses exceeded that of amitriptyline (10 and 20 mg/kg) and fluoxetine (13 mg/kg). [25]

Rhazya stricta

The aqueous extract of leaves of *Rhazya stricta* Decne (Family: Apocynaceae) administered at doses of 0.025–6.4 g/kg *p.o.* showed anti-depressant like effect in male rats employing FST. The antidepressant potential involved the inhibition of MAO. [68]

Rhizoma acori

Decoction of *Rhizoma acori* tatarinowii (Family: Araceae) significantly reduced the immobility time of rats in FST and of mice in TST, thus indicating the antidepressant potential (Li and Chen, 2001). Eugenol, an active principle of *Rhizoma acori* exhibited anti-depressant like activity in mice through the inhibition of both MAO-A and MAO-B. [69]

Rhodiola rosea

The hydro-alcoholic extract of *Rhodiola rosea* L. (Family: Crassulaceae) at the dose of 10, 15 and 20 mg/kg *p.o.* to mice produced significant but non-dose dependent antidepressant-like action. [70]

***Salvia elegans* Vahl**

The hydro-alcoholic extract of leaves and flowers of *Salvia elegans* Vahl (Family: Lamiaceae) showed antidepressant-like activity by decreasing the immobility time of mice and rats subjected to FST. [71]

Scrophularia ningpoensis

Ethyl acetate extract of *Scrophularia ningpoensis* Hemsl. (Family: Scrophulariaceae) roots at the dose of 15 and 20 mg/kg *p.o.* significantly decreased the number of escape failures relative to the control in male ICR mice employing learned helplessness model, thus showed antidepressant-like activity. [44]

Securidaca longepedunculata

Aqueous extract of roots of *Securidaca longepedunculata* (Family: polygalaceae) at the dose of 100, 200, 400 mg/kg, *p.o.* reduced the immobility time of Swiss albino mice when tested in FST and showed significant antidepressant-like action. [72]

Trichilia catigua

The hydro-alcoholic extract of *Trichilia catigua* catuaba (Family: Erythroxylaceae) showed antidepressant-like effect in rats and mice when subjected to FST. The extract also inhibited the uptake and increased the release of serotonin and dopamine from rat brain synaptosomal preparations in a concentration-dependent manner. [73]

Trigonella foneum-graecum

Ethanol and petroleum ether extract of seeds of *Trigonella foneum-graecum* (Family: Leguminosae) at a dose of 50 mg/kg for 7 successive days showed significant anti-depressant-like activity by reducing the immobility period in despair swim test and TST. [74]

Valeriana fauriei

The methanolic extract of *Valeriana fauriei* (Family: Valerianaceae) roots reduced the duration of immobility of male mice in FST and exhibited strong antidepressant-like activity. α -kessyl alcohol and guanine type sesquiterpenoids (kessanol and cyclokessyl acetate) were the active constituents of methanolic extract which were responsible for antidepressant action. [75]

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