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Review Article

An Emerging Role of Herbal Therapy in Depression

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Abstract

Depression is the commonest psychiatric disorders that affect 121 million people world-wide. Depression should be recognized as a clinical syndrome that is characterized by a cluster of emotional, behavioural, and cognitive features. A triad of symptoms clinically characterizes depression: low mood, anhedonia and low energy levels. Other symptoms, such as sleep disturbances, pessimism, guilty feelings, low self–esteem, succidal tendencies, and food- intake dysregulation, are also often present. At present, the choice of medication is completely arbitrary and often based on their side effect profile. Since allopathic medicines attack selected symptoms of depression & exhibit adverse effects, complimentary therapies such as Herbal Therapy are becoming popular. Herbal medicines are widely used across the globe due to their wide applicability and therapeutic efficacy coupled with least side effects, which in turn has accelerated the scientific research regarding the antidepressant activity. The herbal plants and their products (active natural principles and crude extracts) that have been mentioned used in the Indian traditional system of medicine have shown experimental or clinical antidepressant activity. The present review is focued on the medicinal plants having antidepressants activity in animal studies and in humans**.** All these plants possess anti-depressant properties needs to be investigated for those plants that are commonly used in the management of depression. In the search for new molecules useful for the treatment of psychiatric, medicinal plant research, worldwide, has progressed constantly, demonstrating the pharmacological effectiveness of different plant species in a variety of animal's models.

Key Words: Depression, Herbal plants, ethanolic extract, antidepressants.

Introduction

Depression is one among the most rampant form of psychiatric disorders and a leading cause for morbidity and mortality [1]. Misconceptions towards mental disorders and the prevailing stigmatizing attitude among both, the general public and health professionals constitute major barriers in the recovery of mentally ill patients. Depression should be recognized as a clinical syndrome that is characterised by a cluster of emotional, behavioural, and cognitive features. Depression is a common problem affecting about 121 million people world-wide [2]. It occurs in persons of all genders, ages, and back- grounds. Depression is almost twice as common in females as males.

Depression also posses a significant economic burden to society as it leads to reduced productivity, treatment costs and loss of human life by suicide. Lifetime prevalence rates for depression range from 7% to 12% in men and 20% to 25% in women [1]. Depression negatively affects patients' perception of health. How do we now approach depression, a condition that has been identified since antiquity but is still conceptualized as a common and complex disorder of unknown etiology? A triad of symptoms clinically characterize depression: low mood, anhedonia and low energy levels. Other symptoms, such as sleep disturbances, pessimism, guilty feelings, low self–esteem, succidal tendencies, and food- intake dysregulation, are also often present. Because, each of the above symptoms are not qualitatively different from experiences all of us have at some point in our lives, depression is frequently not detected or misdiagnosed. The prevalence of depression is consistently high worldwide, and is associated with considerable morbidity. The disease is more prevalent in women, the female:male ratio being 5:2. There are now dozens of approved drugs, which belong to four different classes-tricyclic drugs, selective serotonin reuptake inhibitors, MAO- inhibitors and miscellaneous antidepressants. Each drug has a success rate of about 60% . When patients do not respond to one particular drug, they are switched to a another one, usually of a different class, until various classes of antidepressants are tried. At present, the choice of medication is completely arbitrary and often based on their side effect profile [3].

Recent estimates have suggested that only 10% patients with depression are likely to receive adequates treatment. It has been repeatedly reported that 40-50 % patients suffering with depression do not seek treatment for their illness. Depression costs the US economy, directly and indirectly, over 43 billion dollars per year and it is a leading cause of disability worldwide. Suicide, which is usually a consequence of depression, is the eighth leading cause of death in the United States. The rate of suicide is even more alarming, when it is examined as a function of age. Suicide is the sixth leading cause of death in the 5–14 age group, the third leading cause of death in the 15–24 age groups, and the fourth leading cause of death in the 25–44 age group. It seems that the incidence of major

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depression is increasing and that the onset of this condition occurs at a younger age now than in previous generations [3]. The patients resort to alternative systems of medicine for depression because they i.) entail a lack of satisfaction with allopathic medicines and/or ii.) they desire to avoid side effects and/or iii.) they are scared of the stigma attached to conventional treatment. Since allopathic medicines attack selected symptoms of depression & exhibit adverse effects, complimentary therapies such as Herbal Therapy are becoming popular [4,5]. During the past few years, herbal therapy has increasingly been used as a tool for the investigation of human cognition and its underlying brain mechanisms. Thus there is a constant need to identify newer natural antidepressants with greater efficacy, fewer side effects and to explore their potential over synthetic antidepressants. Various plants and their extracts have been reported to possess antidepressant-like activity [6]. In the search for new molecules useful for the treatment of psychiatric disorders, medicinal plant research, worldwide, has progressed constantly, demonstrating the pharmacological effectiveness of different plant species in a variety of animals models [5].

Plants Reported to Possess Antidepressant Property

Herbal medicines are widely used across the globe due to their wide applicability and therapeutic efficacy coupled with least side effects, which in turn has accelerated the scientific research regarding the antidepressant activity. Several plants have been explored that possess antidepressant activity [6]. Ayurveda, the oldest medicinal system in the world, provides leads to find therapeutically useful compounds from plants. Therefore, Ayurvedic knowledge supported by modern science is necessary to isolate, characterize, and standardize the active constituents from herbal source. This combination of traditional and modern knowledge can produce better antidepressant drugs with fewer side effects. Plants have been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. Further, the use of herbal medicines is increasing worldwide day by day. Various herbal drugs (e.g. St. John's wort) have shown promising results in treating experimental as well as clinical depression and many of these herbal drugs appear to be safe [7]. We have highlighted some of the important plants reported for their antidepressant properties (Table - 1).

The following herbal plants have been reported to have antidepressant-like activity:

1. **Aloysia polystachya**

The plant is commonly known as Lemon verbena Hydroalcoholic extract (12.5, 25 and 50 mg/kg, i.p.) of the leaves of Aloysia polystachya (Griseb.) Moldenke (Family: Verbenaceae), produced antidepressantlike action in female Sprague-Dawley rats when tested in Forced Swim Test (FST). The efficacy of the extract was comparable to fluoxetine (10 mg/kg, i.p) and imipramine (12.5 mg/kg, i.p.). Thujone and carvone components of the extract were expected to be responsible for antidepressant-like action ([8].

2. **Allium sativum** : It is commonly known as garlic. Garlic is the fresh and dried bulbs of Allium sativum Linn. (Lilliaceae). Fresh and aged extracts of garlic (25, 50 and 100 mg/kg p.o.) administered for 14 successive days to mice decreased immobility periods significantly in a dose-dependent manner as compared to control in both TST and FST, indicating significant antidepressant-like activity. A dose of 100 mg/kg p.o. of fresh extract showed most potent antidepressant effect as indicated by highest decrease in the immobility period. On the other hand, a dose of 50 mg/kg p.o. of aged extract of garlic showed most potent antidepressant-like effect in TST while 100 mg/kg p.o. of aged extract of garlic showed most potent antidepressant-like activity in FST. The efficacy of fresh and aged garlic extracts was found to be comparable to fluoxetine (20 mg/kg) and imipramine (15 mg/kg) administered for two successive weeks in both FST and TST [9].

3. **Apocynum venetum**

The plant is commonly known as Dogbane. Extract of the leaves of Apocynum venetum L. (Family: Apocynaceae) showed significant antidepressant-like action in male rats when tested in FST. This activity of the extract might be related to hyperoside and isoquercitrin which are major the flavonoids. Antidepressant-like activity of the extract, administered chronically for 8 weeks, might be due to interaction with adrenergic and dopaminergic system [10, 11].

4. **Areca catechu**

Ethanolic extract of the fruits of Areca catechu (Family: Arecaceae) showed significant antidepressant-like activity in rats and mice when tested in FST and TST [12]. The dichloromethane fraction from A. catechu showed antidepressant-like activity by inhibiting MAO-A [13].

5. **Anemarrhena asphodeloides**

Sarsasapogenin isolated from Anemarrhena asphodeloides BUNGE (Family: Liliaceae) administered at doses of 12.5, 25 and 50 mg/kg, p.o. for 14 consecutive days to Swiss male mice significantly showed antidepressant-like activity in FST. Sarsasapogenin (50 mg/kg) markedly increased NE and 5-HT levels in hypothalamus and hippocampus. It also inhibited MAO activity in mouse brain. Moreover, sarsasapogenin showed a monoamine oxidase inhibitory activity in the mouse brain. These findings suggest that the antidepressant activity of sarsasapogenin may involve the central monoaminergic neurotransmitter systems. [14].

6. **Annona Cherimolia**

Several species of Annona (Annonaceae) are used in traditional Mexican medicine by their anti-depressants property. It has been reported that the alkaloids isolated from some species of the Annona have affinity to

serotonergic 5-HT1A receptors and modulate dopaminergic transmission, which is involved in depressive disorders [15]. The alkaloid extract from the aerial parts of Annona cherimola showed antidepressant-like effect in forced swimming test in mice. To elucidate a possible mechanism of action, experiments of synergism with antidepressant drugs, such as imipramine (IMI), clomipramine (CLIMI), and fluoxetine (FLX), were carried out. The neurotransmitter content (DA: dopamine, 5HT: serotonin and its metabolites, HVA: homovanillic acid and 5HIAA: 5-hydroxyindoleacetic) in the whole brain of mice were also determined by HPLC method. TA chemical composition was determined using high performance liquid chromatography–electrospray mass spectrometry. The results showed that repeated treatment with Annona produced antidepressant-like effects in mice. Administration of Annona facilitated the antidepressant effect of imipramine and clomipramine as well as increased the turnover of Dopamine and 5-Hydroxy Trytamine. The alkaloids: 1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzoquinoline-3,8,9,10-tetraol, anonaine, liriodenine, and nornuciferine were the main constituents of Annona cherimolia. Annona cherimolia showed that it produces an antidepressant-like action from a generalized increase in monominergic turnover, supporting the use in tradicional medicine and strongly suggest its therapeutic potency as an antidepressant agent [15].

7. **Asparagus racemosus**

It is also called as Shatavari, consists of dried roots and leaves of the plant (Family: Lilliaceae / Asparagaceae). Methanolic extract (50, 100 and 200 mg/kg p.o.) of A. racemosus administered orally for 14 successive days decreased immobility periods significantly in a dose-dependent manner in both TST and FST, indicating significant antidepressant-like activity. The efficacies of the extracts were found to be comparable to fluoxetine and imipramine in both FST and TST. Pretreatment of animals with sulpiride (50 mg/kg) or prazosin (62.5 mg/kg) or p-CPA (100 mg/kg) or baclofen (10 mg/kg) significantly blocked the decrease of immobility time elicited by the extract. Methanolic extract administered for 14 successive days to mice significantly decreased brain MAO-A and MAO-B activities levels as compared to control. Therefore, methanolic extract of Asparagus racemosus showed significant antidepressant-like activity probably by inhibiting MAO-A and MAO-B; and through interaction with adrenergic, dopaminergic, serotonergic and GABAergic systems.[16].

8. **Bacopa monniera**

The plant is commonly known as Brahmi. Bacopa monniera (Family-Scrophulariaceae) is a commonly used Ayurvedic drug for mental disorders. The active constituents are the alkaloids, namely brahmine, herpestine and sponins such as bacoside A and bacosides. The standardized methanolic extract (20 and 40 mg/kg) of B. monniera (bacoside A) orally administered for 5 days to Charles-Foster albino rats (either sex), significantly showed antidepressant-like effect in FST and learned helplessness models. The efficacy of the extract was comparable to imipramine administered at a dose of 15 mg/kg i.p.[17].

9. **Benincasa hispida**

The methanolic extract of the fruits (100 mg/kg, p.o.) of Benincasa hispida (Family- Cucurbitaceae) significantly decreased the immobility periods in both TST and FST, indicating a significant antidepressant-like activity. The efficacy of the extract was found to be comparable to imipramine, fluoxetine, and phenelzine. The study demonstrated that the antidepressant-like effect of the extract was significantly reversed by pretreatment of the animals with sulpiride, baclofen, prazosin, and p-CPA when tested in TST. This suggested that the extract might produce an antidepressant-like effect by increasing the levels of norepinephrine, dopamine, and serotonin, and decreasing the levels of GABA. Drugs which enhance the levels of these monoamines have been used as antidepressant drugs [18].

10. **Camellia sinensis**

The plant is commonly called green tea. The aqueous extract (100 mg/kg) of the leaves of Camellia sinensis (L.) (Family-Theaceae) showed significant antidepressant-like activity in normal, reserpinised (2 mg/kg, i.p.) and diabetic (streptozotocin-induced) male albino laca mice when tested in FST [19].

11. **Canavalia brasiliensis**

The lectins isolated from Canavalia brasiliensis (Family-Leguminosae) seeds (1–10 µg/site, i.c.v.) significantly reduced immobility time of male Swiss albino mice in FST. It also caused the potentiation of fluoxetine action at the dose level of 0.1 µg/site. The antidepressant-like effect involved its interaction with the serotonergic (via 5-HT1A and 5-HT2), noradrenergic (via α2-adrenoceptors) and dopaminergic (via D2 receptors) systems [20].

12. ***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].

13. **Cayratia japonica**

Seven flavonoids (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 C. japonica (Family-Vitaceae) significantly inhibited MAO. Quercetin had a more potent inhibitory effect on MAO-A while apigenin and luteolin preferentially inhibited MAO-A [22].

14. **Cimicifuga racemosa**

The plant is commonly known as Black bugbane. The ethanolic (58% v/v) extract of Cimicifuga racemosa (Family: Ranunculaceae) administered at doses of 25, 50

mg/kg (1 h prior to test) and 100 mg/kg (For 8 days) to female NMRI mice showed significant antidepressant-like action in TST [23].

15**. Cissampelos sympodialis**

Ethanolic extract of the leaves of Cissampelos sympodialis Eichl. (Family: Menispermaceae) at the doses of 20 and 40 mg/kg (i.p) and 125, 250 and 500 mg/kg (p.o.) showed significant antidepressant-like activity in male Swiss albino mice when tested in FST. The extract also reversed the reserpine (16 mg/kg, i.p.) induced ptosis and catalepsy (characteristic of human depression) in rats [24].

16. **Clitoria ternatea**

Clitoria ternatea Linn (Family: Fabaceae) is commonly known as 'Butterfly pea'. The methanolic extract (100 and 400 mg/kg p.o.) of the aerial parts of C. ternatea significantly reduced the immobility time of Swiss albino mice in TST. The antidepressant profile was found to be comparable to fluoxetine administered at a dose of 10 mg/kg i.p. [25].

17. **Convolvulus pluricaulis**

Convolvulus pluricaulis Choisy (Syn. *Convolvulus microphyllus* Sieb ex. Spreng) (family - Convolvulaceae) is also called as Shankhpushpi in India. The chloroform fraction of total ethanolic extract of Convolvulus pluricaulis Choisy (Family: Convolvulaceae), administered 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. The fraction also reversed the reserpine-induced immobility and elicited a significant antidepressant-like effect by interacting with adrenergic, dopaminergic and serotonergic systems. The chloroform fraction of the total ethanolic extract of Convolvulus pluricaulis elicited a significant antidepressant-like effect in mice by interaction with the adrenergic, dopaminergic, and serotonergic systems [26].

18. **Crocus sativus**

The plant is commonly known as Saffron. The hydro-alcoholic extract (30 mg/day TDS and BD) of the stigma of Crocus sativus (Family: Iridaceae) was as effective as imipramine 100 mg/day (TDS) and fluoxetine 20 mg/day (BD) respectively in the treatment of mild to moderate depression in 6 week double blind randomized trial of 40 adult outpatients [27]. Standardized hydro-alcoholic extract of the petals of C. sativus administered for 8 weeks showed antidepressant effect in comparison to placebo in a double blind clinical trial [28].

19. **Curcuma longa**

The plant is commonly known as turmeric. The aqueous extracts of Curcuma longa L. (Family: Zingiberaceae) administered at doses of 140 to 560 mg/kg for 14 days to male ICR mice elicited dose-dependant reduction of immobility time in TST and FST. The extract, at the dose of 140 mg/kg or above for 14 days, significantly inhibited the monoamine oxidase A (MAO-A) activity in mouse whole brain in a dose-dependant manner, however, only at a dose of 560 mg/kg produced significant inhibition of MAO-B activity [29]. The ethanolic extract administered orally for 21 days also reduced the immobility time in FST and it markedly attenuated swim stress-induced decreases in serotonin, Noradrenaline and Dopamine concentrations, as well as increases in serotonin turnover. Furthermore, the ethanolic extract significantly reversed the swim stress-induced increases in serum corticotropin-releasing factor and cortisol levels [76]. Curcumin (5 and 10 mg/kg p.o.) significantly reduced the immobility time in TST and FST, and the antidepressant-like effect may involve the central monoaminergic neurotransmitter systems [77].

20. **Echium amoenum**

Dried flowers of Echium amoenum (Family: Boraginaceae) are used as mood enhancer in Iran. An aqueous extract of E. amoenum (375 mg/day, for 6-weeks) showed antidepressant-like effect in double blind, parallel-group trials of 35 patients [30]. (Sayyah et al., 2006).

21. **Emblica offcinalis**

The Emblica offcinalis Gaertn (Family: Euphorbiaceae) is commonly known as Amla. Aqueous extract (200 and 400 mg/kg) of the fruits was administered orally for 14 successive days to in Swiss young male albino mice employing tail suspension test and forced swim test. The extract significantly decreased immobility period in both tail suspension test and forced swim test, indicating significant antidepressant-like activity. The lower dose (200 mg/kg) of the extract showed better antidepressant-like action. The efficacy of the extract was found to be comparable to fluoxetine (20 mg/kg), imipramine (15 mg/kg), and phenelzine (20 mg/kg). The extract did not show any significant effect on locomotor activity of the mice. Prazosin (alpha1-adrenoceptor antagonist), sulpiride (selective D2-receptor antagonist), baclofen (GABA-B agonist), and p-CPA (tryptophan hydroxylase inhibitor) significantly attenuated the extract-induced antidepressant-like effect. The extract also significantly decreased brain MAO-A levels. The aqueous extract might produce antidepressant-like effect by interaction with α1-adrenoceptors, dopamine D2- receptors, serotonergic, and GABA-B receptors. In this study, aqueous extract was found to contain 2.94% of ascorbic acid. So ascorbic acid and other constituents like flavanoids, tannoid principles, and polyphenolic substances present in the aqueous extract of E. officinalis might be responsible for its antidepressant-like activity. Thus, aqueous extract of E. officinalis showed antidepressant-like activity probably by inhibiting MAO-A and GABA; and also due to its antioxidant activity [31].

22. **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 male Kunming mice reduced the immobility time in FST and

TST. The antidepressant profile was comparable to fluoxetine at dose of 20 mg/kg [32].

23.**Gentiana kochiana**

Diethylether extract of aerial parts of Gentiana kochiana (Family: Gentianaceae) administered 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 [33].

24.. **Ginkgo biloba**

Extract of Ginkgo biloba (14 mg/kg, p.o) (Family: Ginkgoaceae) restored restraint stress-induced decrease in whole brain levels of catecholamines [34]. It also improved the cognitive abilities and sleep disturbances in patients of major depression [78]. Lipophilic extracts of Ginkgo biloba L. leaves were tested for their possible role on rodent models of depression and stress. Lipophilic extracts of Ginkgo leaves (LEG) at (50 and 100 mg/kg, p.o.) exhibited dose dependent, significant antidepressant activity in the behavioral despair test and learned helplessness rodent model of depression [78].

25.**Glycyrrhiza glabra**

The plant is commonly known as Mulethi. Glycyrrhizin (3 mg/kg, i.p., for 7 successive days), an active constituent of Glycyrrhiza glabra L. (Family: Fabaceae), and aqueous extract (150 mg/kg p.o., for 7 successive days) of G. glabra significantly reduced immobility time of male Swiss albino mice when tested in TST and FST. The antidepressant-like action of both glycyrrhizin and aqueous extract was mediated through the interaction with adrenergic and dopaminergic systems. This suggests that antidepressant-like effect of liquorice extract seems to be mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin. Monoamine oxidase inhibiting effect of liquorice may be contributing favorably to the antidepressant-like activity. Thus, it is concluded that liquorice extract may possess an antidepressant-like effect [35]..Ethanolic extract of G. glabra (150 mg/kg, p.o., for 7 successive days) also produced anti-immobolity effect in albino mice (either sex) subjected to FST and TST [36].

26. **Hippeastrum vittatum**

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

27. **Hypericum perforatum** L

Hypericum perforatum L. (Family: Hypericaceae) also called St. John's Wort (SJW) is the only natural herbal alternative to classic synthetic antidepressants in the therapy of mild to moderate depression [38]. It has been known for centuries for its putative medicinal properties, including antidepressant, anxiolytic,diuretic, antibiotic, antimalarial, wound healing and anthelmintic [38]. Hypericum extract, standardized to both hypercin and hyperforin, appears to have significant free radical scavenging properties in cell-free and human vascular system [79]. Hypericum contains numerous compounds with documented biological activity. Constituents that have stimulated the most interest include the naphthodianthrones namely hypericin and pseudohypericin, phlorglucinols namely hyperforin and adhyperforin; flavonoids like flavonol glycosides, viz. Rutin, quercitrin, isoquercitrin, hyperin/hyperoside and aglycones, viz. Kaempferol, xanthones namely kiekorin in roots, 1,3,6,7-tetrahydroxanthone in trace amounts in leaves and stems. 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* and this may be involved in inhibition of uptake of serotonin, noradrenaline and dopamine . 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. Flavonoids like hyperoside, isoquercitrin and miquelianin isolated from the crude extract of H. perforatum showed significant antidepressant-like activity in FST after 12 days of daily treatment [79]. Hydroalcoholic extract of H. perforatum, at doses of 600 mg/day (once daily) and 1200 mg/day (600 mg twice daily) were found to be safe and more effective than placebo in a 6-week double-blind, randomized, placebo-controlled, multi-center clinical trial of 332 patients for the treatment of mild to moderate major depression [80].

28. **Hypericum glandulosum**

The methanol extract of aerial parts of Hypericum glandulosum Ait. (Family: Hypericaceae), butanol and chloroform fractions of methanol extract significantly reduced the immobility time in FST [39, 40]].

29.**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 (either sex) in FST [41].

30. **Hedyosmum brasiliense**

The ethanolic extract of the leaves of Hedyosmum brasiliense exhibits an antidepressant-like effect in the tail suspension and forced swimming tests in mice. H. brasiliense (50 mg/kg, i.p.) and podoandin (10 mg/kg, i.p.) decreased the immobility time in the forced swimming test, without any accompanying changes in ambulation in the open-field test. The anti-immobility effect of the H. brasiliense extract was prevented by pre-treating the mice with ondansetron, pindolol, prazosin, yohimbine, haloperidol, SCH23390, and sulpiride. On the other hand, pre-treating the mice with: p-chlorophenylalanine (4 consecutive days), ketanserin, naloxone, naltrindole, bicuculline, phaclofen, or l-arginine did not block the antidepressant-like effect of H. brasiliense. The antidepressant-like effect of H.

brasiliense (and podoandin) is dependent on the serotonergic, noradrenergic and dopaminergic systems [42].

31.**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 [43].

32.**Kielmeyera coriacea**

Ethanolic extract of the stem of Kielmeyera coriacea Mart. (Family: Clusiacea), administered chronically 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 [44]. The semi-pure dichloromethane fraction (purified by vacuum chromatography) of the ethanolic extract administered at the dose of 5 mg/kg for 45 successive days also significantly reduced the immobility period in FST[45].

33. **Lepidium meyenii**

Aqueous extract (1g/kg/day, p.o.) of hypocotyls of Lepidium meyenii Walp. (Family: Brassicaceae), commonly called Maca, administered to Swiss female ovariectomized mice for 21 consecutive days significantly showed antidepressant like activity in FST [46].

34. **Magnolia officinalis**

The active metabolites such as magnolol and dihydroxydihydromagnolol obtained from the aqueous extract of Magnolia officinalis (Family: Magnoliaceae) bark, administered at dose of 50-100 mg/kg, i.p. to mice, attenuated the forced swim-induced experimental depression [47].

35.**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 Swiss male albino mice subjected to TST [31]. The extract containing approximately 60% mitragynine (a major indole alkaloid) administered at doses of 60 and 90 mg/kg, i.p.) also significantly reduced the immobility time of mice in FST [48].

36. **Morinda officinalis**

The ethanolic extract and oligosaccharides from Morinda officinalis (Family: Rubiaceae) showed antidepressant potential in both mice and rats subjected to FST and learned helplessness paradigm [49]. The aqueous extract (50 mg/kg) of the roots showed antidepressant-like activity in male mice subjected to FST [50].

37. **Myristica fragrans**

The n-hexane extract of Myristica fragrans (Family: Myristicaceae) seeds (5, 10, and 20 mg/kg) administered orally for 3 successive days to male Swiss albino mice significantly decreased immobility time in FST and TST without any significant effect on locomotor activity. The antidepressant-like effect was mediated by interaction with adrenergic, dopaminergic and serotonergic systems [51].

38. Nardostachys jatamansi

Ethanolic extract of *Nardostachys jatamansi* DC. (Family: Valerianaceae), on depression (100, 200 and 400 mg/kg, p.o.) administered for 14 successive days to Swiss young albino mice (either sex) produced significant antidepressant-like effect in both TST and FST. The efficacy of the extract was found to be comparable to imipramine (15 mg/kg, p.o.) and sertraline (20 mg/kg, p.o.). The antidepressant-like effect of ethanolic extract (200 mg/kg) was significantly reversed by pretreatment of animals with sulpiride (a selective dopamine D2-receptor antagonist) and baclofen (GABAB agonist), when tested in TST. This suggested that the antidepressant-like effect of the extract might be due to interaction with dopamine D2-receptor and GABAB receptors, hence increasing the levels of dopamine and decreasing the levels of GABA in mouse brain. The extract also reduced the mouse whole brain MAO-A and MAO-B activities as compared to control, hence exerted antidepressant-like effect by imbibing the metabolism of monoamines. It also significantly reduced the mouse whole brain malondialdehyde levels as compared to control, hence antidepressant-like effect might be due to decrease in lipid peroxidation. Thus, ethanolic extract of *N. jatamansi* showed antidepressant-like activity probably by inhibiting MAO-A, MAO-B and lipid peroxidation, and through interaction with dopaminergic and GABAergic receptors. The extract of *N. jatamansi* may be further studied to find out the particular active component(s) responsible for its antidepressant-like activity. [52].

39. **Ocimum sanctum**

The plant is known as Tulsi. The ethanol extract of the leaves of Ocimum sanctum L. (Family: Labiateae), commonly called Tulsi, significantly decreased the immobility of rats and mice in FST. The antidepressant-like action was blocked by haloperidol and sulpiride, indicating the involvement of dopaminergic neurons [53]. The methanol extract of O. sanctum roots (400 mg/kg, i.p.) increased the mice swimming time and thus suggested its antidepressant-like action [81].

40. **Perilla frutescens**

The leaves of Perilla frutescens (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 component of the extract, also significantly produced anti-immobility effect in FST [54]. Apigenin from P. frutescens showed antidepressant-like activity in FST through dopaminergic mechanisms in the mouse brain [82].

41. **Piper longum**

Piperine, isolated from ethanolic 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 [55].

42. **Piper laetispicum**

The effect of laetispicine, an amide alkaloid isolated from the stems of Piper laetispicum (Piperaceae), in forced swimming, open field, acetic acid writhing and formalin tests in KM mice to assess antidepressant and antinociceptive effects. A significant and dose-dependent decrease in the immobility time, as evaluated by the forced swimming test, was observed after laetispicine administration (38.18, 39.79, 58.77 and 67.28% decreased at the doses of 5, 10, 20, 40 mg/kg, respectively), suggesting an antidepressant effect. In conclusion, we showed that laetispicine possessed significant antidepressant and antinociceptive properties, making this drug potentially useful in depression and pain [56].

43. **Plantago asiatica**

The petroleum extract of Plantago asiatica L. (Family: Plantaginaceae) administered at doses of 5 and 10 mg/kg, p.o. significantly showed antidepressantlike activity in male ICR mice employing learned helplessness model [43].

44.***Polygala tenuifolia***

The polygalatenosides A, B, C, D and E, isolated from the water-soluble extract of the roots of Polygala tenuifolia (Family: Polygalaceae), has antidepressant potential. The polygalatenosides A and B acted as norepinephrine reuptake inhibitors through the blocking of norepinephrine transport [57].

45. **Psoralea corylifolia**

The total furocoumarins from seeds of Psoralea corylifolia L. (Family: Leguminosae) administered at doses of 7.5 to 100 mg/kg, p.o. for 3 successive days significantly decreased the immobility time of male ICR mice employing FST. The efficacy of the higher doses exceeded that of amitryptyline (10 and 20 mg/kg) and fluoxetine (13 mg/kg). The antidepressant potential was mediated via MAO activity, HPA axis and oxidative stress in the FST [58].

46. **Punica granatum**

Juice and seed extract of Punica granatum, commonly called pomegranate, (Family: Lythraceae) administered for 2 weeks to ICR albino ovariectomized mice significantly shortened the immobility time compared with 5% glucose treated mice (control) in FST, hence showed antidepressant-like action [59].

47. **Radix puerariae**

Radix puerariae (root of the Pueraria plant) was first described in the Chinese Materia Medica and Pueraria lobata (Willd.) Ohwi (Family: Fabaceae) is one of the earliest medicinal plant used in China. The radix puerariae extract (75, 150, and 300 mg/kg), administered orally 24 h after cerebral ischemia reperfusion markedly shortened the increased immobility period of male ICR mice, when tested in FST and TST, indicating possible antidepressant-like activity [60].

48. **Rhazya stricta**

The lyophilized aqueous extract of leaves of Rhazya stricta Decne (Family: Apocynaceae) administered at doses of 0.025–6.4 g/kg p.o. showed antidepressant like effect in Wistar male rats employing FST. The antidepressant potential involved the inhibition of MAO [61].

49**. Rosmarinus officinalis**

The plant is known as Rosmemary. Rosmarinus officinalis L. (Labiatae) has several therapeutic applications in folk medicine in curing or managing a wide range of diseases, including depression. The hydroalcoholic extract of Rosmarinus. officinalis produced an antidepressant-like effect, since the acute treatment of mice with the extract by p.o. route significantly reduced the immobility time in the FST (100 mg/kg) and TST (10–100 mg/kg), as compared to a control group, without accompanying changes in ambulation in the open-field test. Moreover, the repeated administration (14 days) of the hydroalcoholic extract of R. officinalis by p.o. route also produced an antidepressant-like effect in the TST (100–300 mg/kg). The results suggest that the antidepressant action of the extract of R. officinalis is mediated by an interaction with the monoaminergic system and that this plant should be further investigated as an alternative therapeutic approach for the treatment of depression [62].

50.**Salvia elegans Vahl**

The hydroalcoholic (60%) 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 [63].

51.**Schinus molle**

Schinus molle L. (Anacardiaceae), among other uses, is popularly employed for the treatment of depression. Hexane extract (30-600 mg/kg p.o.) from leaves of Schinus molle L. (Family: Anacardiaceae) significantly reduced the immobility time of mice in TST. The efficacy was found to be comparable to fluoxetine (10 mg/kg, p.o.) and the anti-immobility effect of the extract (100 mg/kg, p.o.) was prevented by pretreatment of mice with p-chlorophenylalanine methyl ester (pCPA, 100 mg/kg, i.p., an inhibitor of serotonin synthesis, for 4 consecutive days), NAN-190 (0.5 mg/kg, i.p., a 5-HT1A receptor antagonist), ketanserin (5 mg/kg, i.p., a 5-HT2A/2C receptor antagonist), prazosin (1mg/kg, i.p., an α1-adrenoceptor antagonist), yohimbine (1 mg/kg, i.p., an α2-adrenoceptor antagonist), sulpiride (50 mg/kg, i.p., a D2 receptor antagonist). Hence antidepressant-like effect was due to its interaction with the serotonergic, noradrenergic and dopaminergic systems [41]. These results provide evidence that the extract from S. molle shares with established antidepressants some pharmacological effects, at least at a preclinical level. (64).

52.**Scrophularia ningpoensis**

Ethyl acetate extract (15 and 20 mg/kg p.o.) of Scrophularia ningpoensis Hemsl. (Family: Scrophulariaceae) roots significantly decreased the number of escape failures relative to the control in male ICR mice employing learned helplessness model, thus showed antidepressant- like activity [43].

53.**Securidaca longepedunculata**

Securidaca longepedunculata (Family: polygalaceae) is commonly called as violet tree in Nigeria. The aqueous extract of S. longepedunculata (100, 200, 400 mg/kg, p.o.) roots reduced the immobility time of Swiss albino mice (either sex) when tested in FST and showed significant antidepressant- like action [65].

54.**Siphocampylus verticillatus**

The hydroalcoholic (50%) extract of aerial parts (stems and leaves) of S. verticillatus (Family: Campanulaceae) administered at the dose range of 100-1000 mg/kg i.p reduced the immobility time of Swiss female mice in TST and FST. Oral administration of the extract was also effective in TST. Antidepressant-like action involved the interaction with adrenergic, dopaminergic, glutamatergic and serotonergic systems. The anticipated active principle(s) responsible for the antidepressant-like effects of the extract were alkaloids: cis-8,10-di-npropyllobelidiol hydrochloride dehydrate, flavonoids: 3-methoxy luteolin, triterpenes: α-amirin and β-amirin, and steroids: campesterol, β-sitosterol, stigmasterol and stigmasterol glycoside [66].

55. **Tabebuia avellanedae**:

The antidepressant-like effect of the ethanolic extract obtained from barks of Tabebuia avellanedae, a plant widely employed in folk medicine. The extract from T. avellanedae produced an antidepressant-like effect, in the FST (100 mg/kg, p.o.) and in the TST (10-300 mg/kg, p.o.), without accompanying changes in ambulation when assessed in the open-field test. The combination of fluoxetine (1 mg/kg, p.o.), desipramine (0.1 mg/kg, p.o.), or bupropion (1 mg/kg, p.o.) with a subeffective dose of the extract (1 mg/kg, p.o.) produced a synergistic antidepressant-like effect in the TST, without causing hyperlocomotion in the open-field test. It may be concluded that the extract from T. avellanedae produces an antidepressant-like effect in the FST and in the TST that is dependent on the monoaminergic system. The study suggest that T. avellanedae deserves further investigation as a putative alternative therapeutic tool that could help the conventional pharmacotherapy of depression [67].

56. **Terminalia bellirica**

Aqueous (50, 100 and 200 mg/kg) and ethanolic (100 mg/kg) extracts of Terminalia bellirica Roxb. fruits (Family: Combretaceae) significantly reduced the immobility time of Swiss male albino mice in FST and TST. Both the extracts reversed reserpine-induced increase in immobility when tested in TST and FST. The antidepressant effect might be due to interaction with adrenergic, dopaminergic and serotonergic systems [68].

57. **Tinospora cordifolia**

Tinospora cordifolia (Family: Menispermaceae), a well known plant of Indian medicinal system, was possess antidepressant like activity in laboratory animals. The effect of petroleum ether extract of Tinospora cordifolia (Wild.) Miers (50, 100 and 200 mg/kg, p.o.) was administered for 14 successive days to Swiss young albino mice (either sex) and evaluated for antidepressant-like activity using tail suspension test and forced swim test. Petroleum ether extract at all three doses produced significant antidepressant-like effect in tail suspension test as well as in forced swim test and their efficacies were found to be comparable to imipramine (15 mg/kg, p.o.) and sertraline (20 mg/kg, p.o.). The extract at a dose of 50 mg/kg showed most potent effect and did not show any significant change in locomotor functions of mice as compared to control. The antidepressant-like effect of the extract was significantly reversed by pretreatment of animals with prazosin (a α1-adrenoceptor antagonist), sulpiride (a selective dopamine D2-receptor antagonist), p-CPA (a serotonin synthesis inhibitor) and baclofen (GABA-B agonist), when tested in tail suspension test. Moreover, petroleum ether extract also reduced the mouse whole brain monoamine oxidase (MAO-A and MAO-B) activities as compared to control, resulting in increase in the levels of brain monoamines. Therefore, the extract may have potential therapeutic value for the management of depressive disorders [69].

58. **Trigonella foneum-graecum**

Trigonella foneum-graecum (Family: Leguminosae) is commonly called fenugreek. Ethanolic and petroleum ether extract of the seeds of fenugreek administered at a dose of 50 mg/kg for 7 successive days showed significant antidepressant-like activity by reducing the immobility period in despair swim test and TST [70].

59. **Valeriana fauriei**

The methanolic extract of Valeriana fauriei (Family: Valerianaceae) roots reduced the duration of immobility of male mice (ddY strain) in FST and exhibited strong antidepressant-like activity. The α-kessyl alcohol and guanine type sesquiterpenoids (kessanol and cyclokessyl acetate) were the active constituents of methanolic extract which were responsible for antidepressant action [71].

60.**Withania somnifera**

Withania somnifera (Family: Solanaceae), known as Indian ginseng and commonly called ashwagandha has been classified as rasayana in Ayurveda. The bioactive glycowithanolides isolated from W. somnifera roots, when administered at the doses of 20 and 50 mg/kg, p.o. once daily for 5 days, exhibited antidepressant-like effect in FST and learned helplessness paradigms [72]. The root extract (100 mg/kg, i.p.) produced antidepressant-like action in mice through a -adrenoreceptors as well as alteration in the levels of central biogenic amines [73]. Withania somnifera also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim-induced 'behavioral despair' and 'learned

helplessness' tests. The investigations support the use of WS as a mood stabilizer in clinical conditions of anxiety and depression in Ayurveda [73].

60. **Zizyphus Xylopyrus**

Zizyphus xylopyrus (Retz.) Willd. (Family: Rhamnaceae) is found throughout North-Western India, Pakistan and China. Ethanolic extract when administered at an acute dose of 50 mg/kg of body weight (P<0.01) reduced the immobility time by 10 and 15 seconds as compared to the immobility time of control in both the forced swimming test (FST) in rats and tail suspension test (TST) in rats. Zizyphus xylopyrus exerts an antidepressant effect in the forced swimming test (FST) in rats and tail suspension test (TST) in rats [74].

Conclusion

Depression should be recognized as a clinical syndrome that is characterized by a cluster of emotional, behavioral and cognitive features. All the drugs discussed in this review have exhibited significant clinical & pharmacological activity. The natural products, which have been considered, show promising role in acting as antidepressant drugs. More detailed clinical studies are required for the plants showing antidepressants activity in animal studies, so that depression can be treated effectively by use of herbal plants.

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Table 1.
List of medicinal plants having anti-depressants activities

S. No.	Herbal Plant	Family	Plant Part	Reference
1.	Aloysia polystachya	Verbenaceae	Leaves	[8]
2	Allium sativum	Lilliaceae.	Bulbs	[9]
3	Apocynum venetum	Apocynaceae	Leaves	[10,11]
4.	Areca catechu	Arecaceae	Fruit	[12, 13]
5	Anemarrhena asphodeloides	Lilliaceae.	Rhizome	[14]
6	Annona Cherimolia	Annonaceae	Aerial parts	[15]
7	Asparagus racemosus	Lilliaceae / Asparagaceae	Root and leaves	[16]
8	Bacopa Moniera	Scrophulariaceae	Aerial parts	[17]
9	Benincusa Hispida	Cucurbitaceae	Fruits	[18]
10	Camellia sinensis	Theaceae	Leaves	[19]
11.	Canavalia brasiliensis	Leguminosae	Seed	[20]
12	Casimiroa edulis	Rutaceae	Leaves	[21]
13	Cayratia japonica	Vitaceae	Aerial parts	[22]
14	Cimicifuga racemosa	Ranunculaceae	Roots , Rhizomes	[23]
15	Cissampelos sympodialis	Menispermaceae	Leaves	[24]
16	Clitoria ternatea	Fabaceae	Aerial parts	[25]
17	Convolvulus pluricaulis	Convolvulaceae	Whole plant	[26]
18	Cocus sativus	Iridaceae	Stigma and Petals	[27,28]
19	Curcuma longa	Zingiberaceae	Rhizomes	[29]
20.	Echium amoenum	Boraginaceae	Flower	[30]
21	Emblica officinalis	Euphorbiaceae	Fruits	[31]
22.	Gastrodia elata	Orchidaceae	Root	[32]
23.	Gentiana kochiana	Gentianaceae	Aerial parts	[33]
24	Ginkgo biloba	Ginkgoaceae	Leaves	[34]
25	Glycyrrhiza glabra	Fabaceae	Roots	[35]
26.	Hippeastrum vittatum	Amaryllidaceae	Bulb	[37]
27	Hypercium perforatum	Hypericaceae	Aerial parts	[38]
28.	Hypericum glandulosum	Hypericaceae	Aerial parts	[39,40]
29.	Hypericum reflexum L.	Hypericaceae	Aerial parts	[41]
30	Hedyosmum brasliense	Chloranthaceae	Laeves	[42]
31	Ilex pubescens	Aquifoliaceae	Stems	[43]
32	Kielmeyera coriacea	Clusiacea	Stem	[44,45]
33	Lepidum meyenii	Brassicaceae		[46]
34.	Magnolia officinalis	Magnoliaceae	Bark	[47]
35.	Mitragyna speciosa Korth	Rubiaceae	Leaves	[48]

S. No.	Herbal Plant	Family	Plant Part	Reference
36	Morinda officinalis	Rubiaceae	Roots	[49,50]
37.	Myristica fragrans	Myristicaceae	Seed	[51]
38	Nardosachys jatamansi	Valerianaceae	Fruits	[52]
39.	Ocimum sanctum L.	Labiateae	Leaves	[53]
40.	Perilla frutescens	Labiatae	Leaves	[54]
41	Piper longum	Piperaceae	Fruit	[55]
42	Piper laetispicum	Piperaceae	stems	[56]
43	Plantago asiatica	Plantagoinaceae	Leaf	[43]
44	Polygala tenuifolia	Polygalaceae	Roots	[57]
45	Psoralia corylifolia L.	Leguminosae	Seed	[58]
46	Punica granatum	Lythraceae	Seeds	[59]
47.	Radix puerariae	Fabaceae	Root	[60]
48.	Rhazya stricta	Apocynaceae	Leaves	[61]
49	Rosmarinus officinalis	Labiatae	stems and leaves	[62]
50.	Salvia elegans Vahl	Lamiaceae	Leaves, flower	[63]
51.	Schinus molle L.	Anacardiaceae	Leaves	[64]
52.	Scrophularia ningpoensis Hemsl.	Scrophulariaceae	Root	[43]
53.	Securidaca longepedunculata	Polygalaceae	Root	[65]
54	Siphocampylus verticillatus	Campanulaceae	Aerial part	[66]
55	Tabebuia avellanedar	Bignoniaceae	barks	[67]
56.	Terminalia bellirica Roxb.	Combretaceae	Fruit	[68]
57	Tinospora cordifolia	Menispermaceae),	Stems	[69]
58..	Trigonella foneum-graecum	Leguminosae	Seed	[70]
59.	Valeriana fauriei	Valerianaceae	Root	[71]
60.	Withania somnifera L.	Solanaceae	Root	[72]
61.	Zizphas xylopyrus	Rhamnaceae	Leaves	[74]