IJPSR (2021), Volume 13, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 14 March 2021; received in revised form, 17 August 2021; accepted, 23 August 2021; published 01 February 2022

A COMPREHENSIVE REVIEW OF MEDICINAL HERBS USED AS ANTI-DEPRESSANT

Rasika Dnyandeo Bhalke [*1], Mahendra Ashok Giri [2], Yash S. Lodha [1], Komal A. Pawar [1] and Yogesh S. Kulkarni [1]

Sanjivani College of Pharmaceutical [1], Education and Research Kopargaon - 423603, Maharashtra, India.
Rajashri Shahu College of Pharmacy [2], Buldana - 443001, Maharashtra, India.

Keywords:

Herbal remedies, Anti-depressant.

Correspondence to Author:
Dr. Rasika D Bhalke

Sanjivani College of Pharmaceutical, Education and Research Kopargaon - 423603, Maharashtra, India.

E-mail: rasikabhalke@gmail.com

ABSTRACT: Depression is a significant contributor to the global burden of disease and affects people in all communities across the world. Today, depression is estimated to affect 350 million people. The World Mental Health Survey conducted in 17 countries found that, on average, about 1 in 20 people reported having an episode of depression in the previous year. Depressive disorders often start at a young age; they reduce people's functioning and often are recurring. For these reasons, depression is the leading cause of disability worldwide in terms of the total years lost due to disability. Depression is known with some signs, such AS altered cognitive functions and mood, and is linked with a significant social dysfunction such as decreased quality of life. The demand for curbing depression and other mental health conditions is on the rise globally. A recent World Health Assembly called on the World Health Organization and its member states to take action in this path.

INTRODUCTION: Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite and poor concentration. Moreover, depression often comes with symptoms of anxiety. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide. Almost 1 million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day. For every person who completes suicide, 20 or more may attempt to end his or her life. There are multiple variations of depression that a person can suffer from, with the most general distinction being depression in people who have or do not have a history of manic episodes. The depressive episode involves symptoms such as depressed mood, loss of interest and enjoyment, and increased fatigability. Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(2).559-68

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(2).559-68

An individual with a mild depressive episode will have some difficulty in continuing with ordinary work and social activities but will probably not cease to function thoroughly. On the other hand, during a severe depressive episode, it is very unlikely that the sufferer will be able to continue with social, work, or domestic activities, except to

a very limited extent. The bipolar affective disorder typically consists of both manic and depressive episodes separated by periods of normal mood. Manic episodes involve elevated mood and increased energy, resulting in over-activity, the pressure of speech, and decreased need for sleep1.

Pathophysiology:

Monoamine Hypothesis: The first major hypothesis of depression was formulated about 30 years ago and proposed that the main symptoms of depression are due to a functional deficiency of the brain monoaminergic transmitters norepinephrine (NE), 5-HT and/or dopamine (DA), whereas mania is caused by functional excess of monoamines at critical synapses in the brain. Evidence for this hypothesis came from clinical observations and animal experiments, which showed that the antihypertensive drug reserpine, which causes a depletion of presynaptic stores of NE, 5-HT and DA, induced a syndrome resembling depression. In contrast to the effects obtained with reserpine, euphoria and hyperactive behavior were observed in some patients being treated with iproniazid, a compound synthesized for the treatment of tuberculosis, which increased brain concentrations of NE and 5-HT by inhibiting the metabolic enzyme MAO. Considering the origin of the noradrenergic, serotonergic, and dopaminergic neurons in the brain and their projections into many areas of the brain, it is clear that monoaminergic systems are responsible for many behavioral symptoms, such AS mood, vigilance, motivation, fatigue, and psychomotor agitation or retardation. Abnormal function and the behavioral consequences of either depression or the manic state may arise from altered synthesis, storage, or release of the neurotransmitters and disturbed sensitivity of their receptors or subcellular messenger functions.

Transporters for Neurotransmitter Reuptake: Transport proteins play a crucial role in monoaminergic transmission: they reduce the availability of neurotransmitters in the synaptic cleft and thus terminate the effect of the neurotransmitters on pre-and postsynaptic receptors. Although much of our knowledge about transporter dysfunction comes from animal and post-mortem brain studies, the 5-HT transport system is not restricted to tissues of the CNS but is also present in human platelets. This allows us to investigate its function *in-vivo* and in different states of depression. Different substances have been used to mark the protein and other investigations measured the active uptake of 5-HT and at least for platelets; there is no consensus about a decreased transporter function in major depression, a finding that was not observed in other psychiatric disorders. In contrast, the results with post mortem samples are not as convincing as those with platelets, possibly due to inconsistencies in the selection of subjects or the much-discussed problems of investigating the rapidly degrading proteins after various post-mortem delays.

The problems of post mortem investigations may be overcome by functional imaging techniques that allow a noninvasive investigation of the 5-HT transporter in the human brain. Using the method of single-photon emission computed tomography (SPECT) and the radio-labeled tracer 123. I-β-CIT ([123 I]-2 β – carbomethoxy – 3 β - (4-iodophenyl) tropane), the decrease in 5-HT transport that had already been identified in platelets was confirmed for the CNS. 50, 51 Moreover, there might even be a genetic basis for this dysfunctional 5-HT transport since a common polymorphism within the promoter region of the 5-HT transporter gene leads to altered transcriptional activity and hence to diminished expression of the gene. Interestingly, this polymorphism for “lower function” was found more frequently in depressed patients. As regards the NE transporter, few studies have been conducted to measure the NE reuptake sites. Without an ideal peripheral model, most experiments were carried out in post mortem samples, and the few results are controversial. There was also no relationship to genetic variants of the NE transporter.

Neurotransmitter Receptors: In addition to monoamine deficiency, an abnormality in transmission can also arise from changes in receptor function, which means either change in the coupling between transmitters and receptors or changes in the downstream signal transduction cascade. For both the noradrenergic and serotonergic systems, a multiplicity of receptors have been identified so far, each classified according to its pharmacological or molecular characteristics. NE transmission is regulated via α-

or β-adrenoceptors and their various subtypes, with the same pharmacological properties in the brain and periphery [29]. Receptor classification for the serotonergic system has proceeded rapidly, and to date, we know of several major categories, ranging from 5-HT1 to 5-HT7 receptors, each with further subtypes. Receptors are not static entities: their numbers and affinities are regulated by many factors, for example, the transmitter concentration, which leads to compensatory down- or up-regulation in the receptor protein. Despite intensive investigation over the years, our knowledge of alterations in monoamine receptor numbers or affinities in untreated depressed patients is relatively poor and unconvincing.

The frequently reported supersensitivity of pre-synaptic α2-adrenoceptors, which modulate the release of NE, as well as altered numbers and affinities of 5-HT1 and 5-HT2 receptors in the brain and/or platelets, have been the subject of much discussion. Due to the rapid development of molecular biology, interest has shifted from the mere determination of the receptor numbers or affinities toward the signal transduction cascade. There is mounting evidence for the role of these mechanisms in the modulation of neuronal activity and the pathophysiology of mental disorders. Using this new approach, several studies in peripheral cell model systems and/or in post-mortem brain tissue report alterations in G-proteins at multiple sites of the cAMP pathway and in protein kinases. These findings have led to the formulation of a molecular and cellular hypothesis of depression, which proposes that signal transduction pathways are pivotal in the CNS in that they affect the functional balance between multiple neurotransmitter systems and physiological processes [2].

Symptoms:

- Feelings of sadness or unhappiness irritability or frustration.
- Loss of interest or pleasure in normal activities.
- Reduced sex drive
- Insomnia or excessive sleeping
- Changes in appetite depression often cause decreased appetite and weight loss, but in some people, it causes increased cravings for food and weight gain.
- Agitation or restlessness-for example, pacing, hand-wringing, or an inability to sit still.
- Slowed thinking, speaking, or body movements.
- Indecisiveness, distractibility, and decreased concentration.
- Fatigue, tiredness, and loss of energy-even small tasks may seem to require a lot of effort.
- Feelings of worthlessness or guilt, fixating on past failures or blaming yourself when things aren't going right. Trouble thinking, concentrating, making decisions, and remembering things.
- Frequent thoughts of death, dying or suicide, Crying spells for no apparent reason. Unexplained physical problems, such as back pain or headaches.
- Depression affects each person in different ways, so symptoms caused by depression vary from person to person. Inherited traits, age, gender, and cultural background all play a role in how depression may affect you [3].

Herbal Treatment on Depression: There has been an increase worldwide in the use of medicinal plants and herbs for developing nutraceuticals to treat depression and other psychiatric disorders. Medicinal plants in their natural forms are valuable as they are rich in various phytochemical compounds. These phytochemical compounds have pharmacological roles in treating different disease conditions, apart from being widely available in nature and commercially beneficial. The phytochemical compounds in plants are constantly being explored through various experimental studies to determine the molecular basis of how medicinal plants work concerning drugs and diseases and developing nutraceuticals for improving conditions. This review summarizes 27 medicinal plants and their phytochemical constituents that have been shown to possess anti-depressant activity. This review also highlights the

various mechanisms of anti-depressant action of some of these plants and their plant parts like roots, stem, leaves, flowers, fruit or whole plant; phytochemical compounds showing anti-depressant activity such flavonoids, steroids, saponins, sugars, lectins, alkaloids, etc.; and various anti-depressant screening models used such as tail suspension test, forced swim test, chronic un- predictable stress test, sucrose preference test, monoamine oxidase inhibition assay, learned helplessness test, open field test, hole board test, *etc.* However, mechanistic evaluation of many of these plants still needs to be investigated and explored [4].

Herbal Plants Used AS Anti-depressants:

***Apocynum venetum* (word-leaf dogbane):** *Apocynum venetum* is commonly known as the word-leaf dogbane belongs to the family Apocynaceae. It is native to northwestern China. Wu T *et al.* investigated the effects of *A. venetum* leaf extract (AVLE) on depressive behaviors and neuronal apoptosis in a chronic unpredictable mild stress. Results showed that AVLE significantly reduced the immobility time of mice in both the forced swimming test and tail suspension test. AVLE has been shown to increase concentrations of the main neurotransmitters norepinephrine, dopamine, dihydroxy phenylacetic acid, and homovanillic acid in the hippocampus [5].

***Bacopa monnieri* (Brahmi Herb):** *Bacopa monnieri* is commonly known as Brahmi belongs to Plantaginaceae, native to India. Murty Kadali *et al.* evaluated the anti-depressant activity of Brahmi in experimental models in albino mice using forced swimming test, tail suspension test and shock-induced depression. Brahmi at (10, 20, 30 mg/kg) exhibited a significant decrease in duration of immobility in FST and reduced the shock-induced decrease in activity in SID models. It contains a natural phytonutrient which are known as bacosides which is responsible for improving vital neurotransmitter activities [6].

***Berberis aristate* (Indian Barberry):** *Berberis aristate* is commonly known as Indian barberry, belongs to the family *Berberidaceae*. It is native to Asia, Europe, and America. Gautam S *et al.* evaluated the anti-depressant effect of ethanolic extract from Abies webbiana and *Berberis aristata* by using Forced Swimming Test and Tail Suspension Test. Ethanolic extract at 200 mg/kg has shown a significant increase in swimming time and suspension time and decreased immobility time. Anti-depressant activity might be by inhibiting the reuptake of serotonin which acts through Serotonergic receptors (G-protein coupled receptors) as mood elevator [7].

***Bupleurum falcatum* (Sickle-Leaved Hare's-Ear):** *Bupleurum falcatum* is also known as sickle-leaved hare's-ear belongs to the family *Apiaceae*. It is native to Europe and Western Asia. Kwon S *et al.* studied the antidepressant-like effect of methanolic extract and its neuropharmacological mechanism in mice. After oral administration of the extract, a tail suspension test (TST) and open field test (OFT) were performed to assess the anti-depressant activity and psychostimulant side effects, respectively. Mechanism of action for anti-depressant activity is the involvement of the serotonergic and noradrenergic/dopaminergic systems [8].

***Camellia sinensis* (White Tea):** *Camellia sinensis* is commonly known as White tea, belongs to the family Theaceae. It is native to East Asia, the Indian Subcontinent, and Southeast Asia. Mamun M *et al.* investigated the anti-depressant activity of the ethanolic extract of white tea (EEWT) by using hole cross test, open field test, and thiopental induced sleeping time test in swiss albino mice. Results demonstrated that the administration of 300 mg per kg body weight dose of EEWT has anti-depressant properties. The dose-dependently reduced sleep induced by thiopental, suggesting that the extract of white tea did not possess a sleep-inducing property. "Thiopental" is basically a hypnotic agent, given at an appropriate dose, induced hypnosis by potentiating GABA mediated postsynaptic inhibition through allosteric modification of GABAA receptors. As measured by hole cross and open field tests, the study on locomotor activity showed that ethanolic extract from the leaves increased the frequency and amplitude of movements. The dose of 300 mg/kg body weight significantly raised the locomotion in mice [9].

***Clitoria ternatea* (Clitoria Ternatea):** *Clitoria ternatea* plant is commonly known as 'butterfly pea belongs to the family *Fabaceae*. It is native to

Africa, Australia, and the Americas. Parvathi M *et al.* investigated the anti-depressant activity of ethanolic root extract of *C. ternatea* Linn. (by Tail suspension test and Forced swimming test), motor coordination (by Rota-rod method), and locomotor (with an actophotometer) models. Results revealed that the extracts were able to reduce the immobility time of rats in a dose-dependent manner. *C. ternatea* contains tannin; the anti-depressant activity may be due to MAO inhibition, thereby increasing norepinephrine and dopamine levels in the brain [10].

***Emblica officinalis* (Indian Gooseberry):** *Emblica Officinalis* is commonly known as Indian gooseberry, belongs to the family *Euphorbiaceae*. It is native to Pakistan, Uzbekistan, Sri Lanka, Southeast Asia, China, and Malaysia. Pemminati S. *et al.* evaluated the anti-depressant potential of acute and chronic administration of *E. Officinalis* in forced swim test and tail suspension test Inbred adult male Swiss Albino mice. The anti-depressant activity of *E. officinalis* was comparable to that of standard drug imipramine, which significantly reduced the duration of the immobility in both experimental models as compared to control [11].

***Foeniculum vulgare* (Fennel):** *Foeniculum vulgare* is commonly known as Fennel, belongs to the family *apiaceae*. It is native to southern Europe and Asia. Tahira Parveen *et al.* studied anti-depressant effects of fennel oil by comparing it with a synthetic anti-depressant drug, fluoxetine. Struggling time in the forced swim test, the number of squares crossed in the open field test, and time spent in open arm in an elevated plus maze (EPM) was monitored weekly. Repeated administration of fennel oil for 3 weeks showed significant anti-depressant- and anxiolytic-like effects in FST and EPM, respectively, comparable to fluoxetine. *F. vulgare* includes anethole, fenchone, estragole, and limonene. Anethole was reported to particularly inhibit the activity of monoamine oxidase B (MAO-B) enzyme [12]. Saeid Abbasi-Maleki *et al.* studied the anti-depressant potential of *Foeniculum vulgare* essential oil (FVEO), and the contribution of monoaminergic systems to this effect was evaluated in mice using the forced swim test. Different doses of FVEO induced antidepressant-like effects without any alteration in locomotion in the open field test. The anti-depressant like the effect of FVEO on mice demonstrated in the FST, was induced, at least partly by dopaminergic and serotonergic systems, but not to the noradrenergic system. Antioxidants were found to raise 5-HT levels in the synaptic cleft. Moreover, the fennel extract was found to increase 5-HT levels in the brain as most of its constituents were found as antioxidants like anethol, limonene, and α- thujone [13].

***Ginkgo biloba* (Maidenhair Tree):** *Ginkgo biloba*, also known AS the maidenhair tree, belongs to Ginkgoaceae. *Ginkgo biloba* is native to China. Rojas P *et al.* studied the antidepressant-like effect of a Ginkgo biloba extract in forced swimming test and spontaneous locomotor activity in mice. Animals were sacrificed to evaluate lipid peroxidation, different antioxidant enzyme activities, serotonin and dopamine content in the midbrain, hippocampus, and prefrontal cortex. Results demonstrated that extract at 10 mg/kg treatment produced a significant reduction (39%). This anti-depressant-like effect of the extract was associated with a reduction in peroxidation and superoxide radical production. It has been shown that extract regulates the dopaminergic and serotonergic uptake systems [14].

***Glycyrrhiza glabra* (Licorice):** *Glycyrrhiza glabra* belongs to the family *Fabaceae*, commonly known AS licorice. It is native to Eurasia, in central and south-western Asia and the Mediterranean region. Dhingra D *et al.* investigated the effects of aqueous extract of *G. glabra* on depression in mice using forced swim test and tail suspension test. *G. glabra* produced an antidepressant-like effect in mice in both FST and TST, and this effect seems most likely to be mediated through an interaction with adrenergic and dopaminergic systems [15].

***Hypericum glandulosum* (St. John's Wort):** It is commonly known as St. John's wort, belongs to the family Hypericaceae, and is native to North America and eastern Asia. Bonkanka CX. *et al.* studied the effect of the aqueous, butanol, and chloroform fractions obtained from the methanol extracts of these Hypericum species in mice particularly forced swimming test. Results revealed that immobility time in the forced swimming test was significantly reduced. Chloroform extract from *Hypericum glandulosum* at 500 mg/kg p.o. in the

forced swimming test was comparable to that of the tricyclic anti-depressant imipramine. *H. glandulosum* causes significant effects in antagonizing the tetrabenazine-induced ptosis at the dose applied, which usually evidences a certain alpha-adrenergic or serotoninergic activity [16].

***Ilex paraguariensis* (Yerba Mate):** *Ilex paraguariensis* is commonly known as Yerba Mate. Native to South America which grows in Brazil, Argentina and Paraguay. Reis EDM. *et al.* investigated the possible antidepressant-like effect of *I. paraguariensis* in rats. After treatment, behavioural (elevated plus-maze, open field test, and forced swimming test) and biochemical parameters (lipid peroxidation assay, thiol content, vitamin C levels, and monoamine oxidase activity) were evaluated. Aqueous extract of *I. paraguariensis* decreases the time of immobility in rats suggesting an antidepressant-like effect. *I. paraguariensis* reduced the immobility time on forced swimming test without significant changes in locomotor activity in the open field test. Any anxiolytic/anxiogenic effect of *I. paraguariensis* was observed in rats through the elevated plus-maze test. The antidepressant-like effect of *I. paraguariensis* was not accompanied by an inhibitory effect on monoamine oxidase activity. There were no significant alterations in lipid peroxidation, thiol content, and vitamin C levels among the groups. In conclusion, aqueous extract of *I. paraguariensis* decreases the time of immobility in rats suggesting an antidepressant-like effect [17].

***Lepidium meyenii* (Maca):** *Lepidium meyenii* is commonly known AS Maca. Belongs to family Brassicaceae Cheng A. *et. al.* studied behavior and anatomical and biochemical effects of petroleum ether extract from maca (ME) in the chronic unpredictable mild stress (CUMS) model of depression in mice at three different doses of maca extract (125, 250, and 500 mg/kg). Results showed that Maca extract (250 and 500 mg/kg) significantly decreased the duration of immobility time in the tail suspension test and induced a significant reduction in corticosterone levels in mouse serum. In mouse brain tissue, after six weeks of treatment, noradrenaline and dopamine levels were increased, and the activity of reactive oxygen species was significantly inhibited. Serotonin levels were not significantly altered. These results demonstrated that maca extract (250 and 500 mg/kg) showed antidepressant-like effects and was related to the activation of both noradrenergic and dopaminergic systems and attenuation of oxidative stress in the mouse brain [18].

***Matricaria recutita* (Chamomile):** Chamomile is *Matricaria recutita* belonging to the family *Asteraceae*. It is an herb that is native to Europe, Africa, and Asia and is now also grown in North America. It may provide anti-depressant activity in anxious, depressed humans. Abdolrasoul N. *et al.* evaluated the anti-depressant activity of *M. chamomilla* and *M. officinalis* in mice through the forced swim test. The mechanism of the anti-depressant effects of ethanolic extracts is unknown, but it seems that flavonoids such AS apigenin, naringenin, quercetin, chrysin, catechins acid, epicatechin, kaempferol, and fisetin can have a preventive effect against monoamine oxidases.

The strongest inhibitors of the combination of ligand and benzodiazepine receptors can be used as anti-depressants. Furthermore, flavones can bind to GABA-A, which can have soothing and relaxing effects. Dietary flavonoids have multiple neuroprotective actions in central nervous pathophysiological conditions, including depression, and it was reported that naringenin can cause a potent antidepressant-like impact via central serotonergic and noradrenergic systems [19]. Radu *et al.* investigated the effects of the M. chamomilla (chamomile) hydroalcoholic extract on anxiety and depression using a scopolamine rat model. Behavioral procedures for anxiety and depression were assessed in rats using an elevated plus maze and forced swimming tests. Results revealed that the extract abolishes scopolamine-induced increases in anxiety and depressive-like responses and exhibited therapeutic benefits for the management of psychological ailments [20].

***Melissa officinalis* (Lemon Balm):** Lemon balm is *Melissa Officinalis* belongs to the family Labiatae and is native to Spain and Europe. Emamghoreishi. *et. al.* .studied the effect of subchronic administration of different doses of and essential oil on immobility, climbing, and swimming behaviours were evaluated in the forced swimming

test. The aqueous extract produced a significant reduction in immobility along with an increase in climbing behaviour. The mechanism of the anti-depressant effect of the aqueous extract is might be by enhancement of norepinephrine neurotransmission. It could be suggested that its anti-depressant effect may be due to the content of tannins, saponins, citral, and rosmarinic acid [21].

***Mimosa pudica* (Touch-Me-Not):** *Mimosa pudica* is commonly known as touch-me-not, belongs to the family Fabaceae, and is native to the Americas and Africa. Udyavar S *et al.* evaluated the potential anti-depressant activity of ethanolic extract of *Mimosa pudica* leaves on depression in Swiss Albino mice. The study showed a significant reduction in immobility time in both forced swim test and tail suspension test in the ethanolic extract group when compared with the control group. Ethanolic Extract of *Mimosa pudica* has anti-depressant activity and can be considered for use in therapy of depression after further testing. The anti-depressant action of ethanolic extract of *Mimosa pudica* is probably similar to the mechanisms of anti-depressant agents, like imipramine that is inhibition of norepinephrine transporter and serotonin transporters, increasing their availability at synaptic cleft, thereby reducing depression [22].

***Mitragyna speciosa* (Kratom):** *M. speciosa* is commonly known as kratomnative to Southeast Asia. It is indigenous to Thailand, Indonesia, Malaysia, Myanmar. Idayu NF *et. al.* studied the anti-depressant effect of mitragynine in the mouse forced swim test and tail suspension test, two models predictive of anti-depressant activity and the effect of mitragynine towards the neuroendocrine system of the hypothalamic-pituitary-adrenal (HPA) axis by measuring the corticosterone concentration of mice exposed to above tests. Mitragyline at dose of 10 mg/kg and 30 mg/kg significantly reduced the immobility time of mice in forced swim test and tail suspension test without any significant effect on locomotor activity in the open field test. Antidepressant-like action of mitragynine might be through the restoration of monoamine neurotransmitter levels, including serotonin, noradrenaline, and dopamine in mice [23].

***Nardostachys jatamansi* (Muskroot):** *Nardostachys jatamansi* (NJ) is also called spikenard, nard, Nardin, or muskroot belongs to the family *Caprifoliaceaean* is native to Himalayas. Wang Z *et. al.* studied anti-depressant effects of total methanol extract of NJ by tail suspension test and open field test. Fractions are also tested. Results revealed that fraction NJFr. 01 was enriched with serotonin transporter enhancing constituents. NJFr. 01 comprises of chlorogenic acids, 8α dihydrogeniposide, 7 deoxy 8 epi-loganic acid, adoxosidic acid, 8-epi-loganic acid, 8α-6,7 dihydroapodantheroside acetate and 6 acetylpatrinalloside [24].

***Ocimum sanctum* (Holy Basil):** Holy Basil is *Ocimum sanctum* native to India. Manu G *et al.* studied the effect of ethanolic extract of leaves of O. Sanctum in the specific doses significantly reduced the immobility time ($p < 0.05$) in both forced swimming test model and tail suspension test models. The alcoholic extract of leaves of *O. Sanctum* has significant anti-depressant activity in acute animal models of depression, and it is comparable with the standard drug imipramine. *O. sanctum* had a normalizing action on noise stress-induced alteration in brain monoamine neurotransmitters (norepinephrine, epinephrine, dopamine, and serotonin) and controlled the alteration in neurotransmitter levels due to stress [25].

***Passiflora incarnate* (Maypop/ Purple Passion Flower):** Maypop/ Purple Passion Flower is *Passiflora incarnate* (PI) mostly found in Central or South America and some species occurring in North America, Southeast Asia, and Australia. Maleki SA *et al.* investigated the anti-depressant effect of hydroalcoholic extract of PI in forced swim test and tail suspension test in male mice. Immobility, swimming, and climbing behaviors were recorded. All doses of PI extract compared to the control group significantly reduced the duration of immobility time in both of the two tests ($p<0.001$). These extracts increased swimming time ($p<0.001$) without significant change in climbing time. PI has a considerable antidepressant-like effect in animal models of depression. It is seen in these studies that hydroalcoholic extract of PI has the serotonergic mechanism as fluoxetine reduces the time immobility, increases the swimming time without any significant change of climbing time [26].

***Panax ginseng* (Asian Ginseng):** *Panax ginseng* is

commonly known AS Asian ginseng, belongs to the family *Araliaceae*. It is Native to China, Russia, and China. Choi JH *et al.* examined the anti-depressant effect and underlying mechanism of *P. ginseng* extract (PGE) in chronic restraint stress (CRS)-induced depression model in mice. After CRS induction, oral administration of Panax ginseng extract for 14 d decreased immobility (depression-like behaviors) time in forced swim and tail suspended tests. PGE enhanced messenger RNA expression level of brain-derived neurotrophic factor but ameliorated microglial activation and neuroinflammation (the messenger RNA and protein expression level of cyclooxygenase-2 and inducible nitric oxide) synthase) in the amygdala of mice after CRS induction. Interestingly, 14-d treatment with celecoxib, a selective cyclooxygenase-2 inhibitor, and Nu-nitro-L-arginine methyl ester hydrochloride, a selective inducible nitric oxide synthase inhibitor, attenuated depression-like behaviors after CRS induction. Additionally, PGE inhibited the upregulation of the nuclear factor erythroid 2 related factors 2 and heme oxygenase-1 pathways [27].

***Rosmarinus officinalis* (Rosemary):** *Rosmarinus officinalis*, commonly known as rosemary, is an evergreen perennial shrub belonging to the *Lamiaceae* family native to the Mediterranean region; rosemary is now cultivated all around the world. Naji H *et al.* studied the potential effects of *R. officinalis* in the treatment of depression in comparison to imipramine by using the forced swimming test, and the immobility and swimming times were measured. Anti-depressant action of *R. officinalis* extract may be mediated by an interaction with the monoaminergic system. The anti-depressant action of R. officinalis also attributed to the luteolin, carnosic acid, and rosmarinic acid. These compounds can cause up-regulated of the two major genes (tyrosine) hydroxylase and pyruvate carboxylase) involved in the regulations of dopaminergic, serotonergic, and GABAergic pathways [28].

***Terminalia arjuna* (Arjuna):** Arjuna is *Terminalia arjuna*. Usually found growing on river banks or near dry river beds in Uttar Pradesh, Bihar, Maharashtra, Madhya Pradesh, West Bengal, Odisha, and south and central India, along with Sri Lanka and Bangladesh. Shahriar M *et al.* studied the neuropharmacological activity by using the forced swimming test and open field test. In the forced swimming test, the methanol extract at a dose of 150 mg/kg showed decreased immobility time like the standard imipramine, indicating its anti-depressant effect. Methanol extract at a dose of 100 mg/kg also showed some anti-depressant activity. It seems that the anti-depressant potential of the extract, suggested by the forced swimming test, is a result of serotonin reuptake inhibition [29].

***Tinospora cordifolia* (Giloy):** *T. cordifolia* is also known as Giloy, belongs to the family Menispermaceae. It is native to Asia, Africa, and Australia. Dhingra D *et al.* investigated the effect of petroleum ether extract of *Tinospora cordifolia* (Wild.) on depression in mice. The extract was given in different concentrations to mice and evaluated for antidepressant-like activity using tail suspension and forced swim tests. Petroleum ether extract at different doses produced a significant antidepressant-like effect in the tail suspension test and forced swim test. Their efficacies were found to be comparable to imipramine and sertraline. Petroleum ether extract also reduced the mouse whole brain monoamine oxidase (MAO-A and MAO-B) activities as compared to control, increasing the levels of brain monoamines. This suggested that the petroleum ether extract might produce an antidepressant-like effect by interaction with α1-adrenoceptors, dopamine D2-receptors, serotonergic and GABA-B receptors, increasing the levels of norepinephrine, dopamine, and serotonin; and decreasing the levels of GABA in brains of mice [30].

***Valeriana officinalis* (Garden Heliotrope):** Garden heliotrope is *Valeriana officinalis* belongs to *Caprifoliaceae* family. It is endogenous to Europe and Asia and widely introduced in North America. Neamati A *et al.* studied the effect of *V. Officinalis* L. hydroalcoholic extract on depression-like behaviour in ovalbumin sensitized rats where rats were treated by 50, 100, and 200 mg/kg dose in forced swimming test and immobility time was recorded. The results showed that the hydroalcoholic extract of *V. officinalis* prevents depression-like behavior in ovalbumin sensitized rats. Many potential mechanisms for the pharmacological action of *V. officinalis* L. have

been proposed based on their agonistic effects through GABA, adenosine, barbiturate and benzodiazepine receptors. It has been shown that valerian increases serotonin concentrations in the brain. Valeric acid is an important component of *V. Officinalis* L., which has been shown to inhibit the breakdown of GABA in the central nervous system [31].

***Withania somnifera* (Ashwagandha):** Ashwagandha is *Withania somnifera* belongs to the family Solanaceae and is native to India. Jayanthi MK *et al.* studied the anti-depressant activity of *Withania somnifera* (AGG) using 3 models, behavioral despair tests- forced swim test, tail suspension test, and anti-reserpine test at different doses like 20, 40 mg/kg. AGG produced a dose-dependent decrease in immobility time in chronic studies in the FST and TST model, with the maximum effect observed with 40 mg/kg. On anti-reserpine models, ptosis, catatonia, and sedation scores in the standard, test, and combination drug groups were significantly different from the control group.

The positive effect of these drugs in FST and TST seems to be due to the increased availability of these neurotransmitters at the postsynaptic receptor sites following their reuptake inhibition [32]. Bhattacharya SK *et al.* investigated the anxiolytic and anti-depressant actions of the bioactive glycowithanolides isolated from roots in rats. Results showed that glycol with anolides induced an anxiolytic effect, comparable to that produced by lorazepam, in the elevated plus-maze, social interaction and feeding latency in an unfamiliar environment tests. Glycowithanolides and lorazepam, reduced rat brain levels of tribulin, an endocoid marker of clinical anxiety, when the levels were increased following administration of the anxiogenic agent, pentylenetetrazole. Glycowithanolides also exhibited an anti-depressant effect, comparable with that induced by imipramine, in the forced swim-induced 'behavioral despair' and learned helplessness tests. The investigations support the use of Withania SA a mood stabilizer in clinical conditions of anxiety and depression in Ayurveda. Neurochemical investigations on Withania root extract indicate that it has significant GABA-mimetic activity in the rodent brain. Thus, Withania extract produced inhibition of (3H) GABA and (355) r-butylbicyclophosphorothionate (TBPS) binding, with a concomitant increase in (3H) flunitrazepam binding to their respective receptor sites in rat brain membranes. The extract also increased 36c1 influx in mouse spinal cord neuron preparation in the absence of GABA. The increased influx was attenuated by the GABA receptor antagonists bicuculline and picrotoxin [33].

***Ziziphus jujuba* (Common Jujube):** *Ziziphus jujuba* is commonly known as common jujube belongs to the family *Rhamnaceae*. It is native to China. Oh JM *et al.* studied the antidepressant-like activity of ethanol extract of *Ziziphus jujuba* Mill var. Spinosa seeds (Semen Ziziphi Spinosa, SZS) by behavioral tests, such AS A forced swimming test, a tail-suspension test, and an open-field test, using mice exposed to chronic unpredictable mild stress the SZS ethanol extract exhibited significant antidepressant-like effects *via* immobility decrease, distance increase, hippocampal NE and 5-HT increase and BDNF expression. These results suggest that the extract could be a potential anti-depressant agent [34].

ACKNOWLEDGEMENT: Authors acknowledge the management of Sanjivani College of Pharmaceutical Education and Research Kopargaon.

CONFLICTS OF INTEREST: Authors declare no conflict of interest.

REFERENCES:

1. SD Reed, EJ Ludman, KM Newton, LC Grothaus, AZ LaCroix and L Nekhlyudov: Depressive symptoms and menopausal burden in the midlife. Maturitas 2009; 62: 306-10.
2. A Fiske, JL Wetherell and M Gatz: Depression in older adults. Annu Rev Clin Psychol 2009; 5: 363-89, https://doi.org/10.1146/annurev. clinpsy.032408.153621
3. Bhowmik D, Sampath Kumar KP, Srivastava S, Paswan S and Dutta AS: The pharma innovation depression - symptoms, causes. Medications and Therapies 1(3): 2012.
4. Martins J and Brijesh S: Phytochemistry and pharmacology of anti-depressant medicinal plants: A review. Biomed Pharmacother 2018; 104: 343-65.
5. Wu T, Li X, Li T, Cai M, Yu Z and Zhang J: *Apocynum venetum* Leaf Extract Exerts Antidepressant-Like Effects and Inhibits Hippocampal and Cortical Apoptosis of Rats Exposed to Chronic Unpredictable Mild Stress 2018; 2018.
6. Murty Kadali SR, Das MC, Srinivasa Rao ASR and Karuna SG: Anti-depressant activity of brahmi in albino mice. J Clin Diagnostic Res 2014; 8(3): 35-7.

7. Gautam S, Sachan N, Shrivastav A and Pal D: Journal of drug delivery and therapeutics evaluation of anti-depressant activity of ethanolic extract of abies webbiana and berberis aristata in. Laborato Anim 2019; 9(1): 244-7.
8. Kwon S, Lee B, Kim M, Lee H, Park H and Hahm D: Progress in neuro-psychopharmacology & biological psychiatry antidepressant-like effect of the methanolic extract from *bupleurum falcatum* in the tail suspension test. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34(2): 265-70.
9. Mamun M, Rashid U, Sayeed MA, Jainul MA and Azam S: Anti-depressant and antibacterial activities of *camellia sinensis* (white tea). e-Journal of Science & Technology (e-JST). 2013; 8(4): 39-46.
10. Parvathi M and Ravishankar K: Evaluation of Antidepressant, Motor Coordination and Locomotor activities of ethanolic root extract of *clitoria ternatea*. Journal of Natural Remedies 2013; 13(1): 19-24.
11. Pemminati S, Shenoy AK and Sahu S: Anti-depressant activity of aqueous extract of fruits of *Emblica officinalis* in mice. International Journal of Applied Biology and Pharmaceutical Technology 2010; 1(2): 448-54.
12. Perveen T, Emad S, Medical J, Muddasir S and Batool Z: Fennel oil treatment mimics the anti-depressive and anxiolytic effects of fluoxetine without altering the serum cholesterol levels in rats. Pak J Zool 2017; 49(6); 2291-97.
13. Abbasi-maleki S and Gholamreza S: Antidepressant-like effects of *Foeniculum vulgare* essential oil and potential involvement of dopaminergic and serotonergic systems on mice in the forced swim test. Pharma Nutrition Pharma Nutrition 2021; 15: 100241.
14. Rojas P, Serrano-garcía N, Medina-campos ON, Pedraza-chaverri J, Ogren SO and Rojas C: Neurochemistry international antidepressant-like effect of a ginkgo biloba extract (egb761) in the mouse forced swimming test : role of oxidative stress. Neurochem Int 2011; 59(5): 628-36.
15. Dhingra D and Sharma A: Antidepressant-like activity of *Glycyrrhiza glabr*a L . in mouse models of immobility tests 2006; 30: 449-54.
16. Bonkanka CX, Prado B and Rabanal RM: Anti-depressant properties of some *Hypericum canariense* L. and *Hypericum glandulosum* Ait extracts in the forced swimming test in mice 2005; 97: 541-7.
17. Reis EDM, Neto FWS, Cattani VB, Peroza LR, Busanello A Leal CQ: Antidepressa andnt-like effect of ilex paraguariensis in rats. Biomed Res Int 2014; 1-9.
18. Cheng A: Antidepressant-like behavioral, anatomical, and biochemical effects of petroleum ether extract from maca (*lepidium meyenii*) in mice exposed to chronic unpredictable mild stress. J Med F 2014; 17(5): 535-42.
19. Namjou A, Yazdani N, Abbasi E and Rafieian-Kopaei M: The anti-depressant activity of matricaria chamomilla and melissa officinalis ethanolic extracts in non-reserpinized and reserpinized Balb/C Mice. Jundishapur J Nat Pharm Prod 2018; 13(4): e65549.
20. Ioniță R, Postu PA, Cioancă O, Mircea C, Hăncianu M and Hrițcu L: Anxiolytic and anti-depressant effects of matricaria chamomilla hydroalcoholic extract in a rat model of scopolamine. Farmacia 2019; 67(1): 68-72.
21. Emamghoreishi M and Talebianpour MS: Anti-depressant effect of *melissa officinalis* in the forced swimming test. Daru 2009; 17(1): 42-7.
22. Udyavar S, K SK, Rai M, Gopalakrishna HN, Chandrashekar R: Evaluation of anti-depressant activity of ethanolic extract of *Mimosa pudica* in swiss albino mice. 2021; 7(4): 244-4.
23. Idayu NF, Hidayat MT, Moklas MAM, Sharida F, Raudzah ARN and Shamima AR: Phytomedicine antidepressant-like effect of mitragynine isolated from *Mitragyna speciosa* Korth in mice model of depression. Eur J Integr Med 2011; 18(5): 402-7.
24. Li R, Wang Z, Wang Y, Dong X, Zhang L and Wang T: Jo ur na l P re. J Ethnopharmacol 2020; 113601.
25. Manu G, Hema NG and Parashivamurthy BM: Study of correlation of antidepressive effects effec of ethanolic leaf extract of O *Ocimum cimum* sanctum and imipramine in albino mice 2015; 13: 472-7.
26. Maleki SA: Evaluation of antidepressant-like effect of hydroalcoholic extract of *Passiflora incarnata* in animal models of depression in male mice. J Herb Med Pharmacol J homepage J Herb Med Pharmacol 2014; 3(1): 41-5.
27. Choi JH, Lee MJ, Jang M, Kim H, Lee S and Lee SW: *Panax ginseng* exerts antidepressant-like effects by suppressing neuroinflammatory response and up-regulating nuclear factor erythroid 2 related factor 2 signaling in the amygdala. J Ginseng Res 2018; 42(1): 107-15.
28. Naji H: Antidepressant-Like effect of *rosmarinus officinalis* extract in male mice. Med J Babylon 2013; 10(4): 803-8.
29. Shahriar M, Saiful I, Robin KA, Aminul H, Shahdaat S and Fahim K: Evaluation of the analgesic and neuropharmacological activities of the bark of *terminalia arjuna* in mice. Int J Recent Sci Res 2013; 4(3): 285-9.
30. Dhingra D and Goyal PK: Evidences for the involvement of monoaminergic and gabaergic systems in antidepressant-like activity of tinospora cordifolia in mice. Indian J Pharm Sci 2008; 70(6): 761-767.
31. Neamati A, Chaman F, Hosseini M and Boskabady MH: The effects of *Valeriana officinalis* L. hydroalcoholic extract on depression like behavior in ovalbumin sensitized rats. J Pharm Bioallied Sci 2014; 6(2): 97-103.
32. Jayanthi MK, Prathima C, Huralikuppi JC, Suresha RN and Dhar M: Anti-depressant effects of *Withania somnifera* fat (*Ashwagandha Ghrutha*) extract in experimental mice. Int J Pha Bio Sci 2012; 3(1): 33-42.
33. Bhattacharya SK, Bhattacharya A, Sairam K and Ghosal S: Anxiolytic-antidepressant activity of *Withania somnifera* glycowithanolides: An experimental study. Phytomedicine. 2000; 7(6): 463-9.
34. Oh JM, Ji M, Lee M, Jeong GS, Paik M and Kim H: Applied sciences antidepressant-like e ff ects of ethanol extract of *ziziphus jujube.* Mill Seeds in Mice 2020; 1-12.

How to cite this article:
Bhalke RD, Giri MA, Lodha YS, Pawar KA and Kulkarni YS: A comprehensive review of medicinal herbs used as antidepressant. Int J Pharm Sci & Res 2022; 13(2): 559-68. doi: 10.13040/IJPSR.0975-8232.13(2).559-68.