



Received on 31 March 2019; received in revised form, 16 June 2019; accepted, 28 June 2019; published 01 January 2020

EMERGING MECHANISMS AND POTENTIAL ANTIDEPRESSANT ACTION OF MEDICINAL PLANTS

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Keywords:

Depression,
Endogenous molecules,
Medicinal plants, Phytoconstituents

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ABSTRACT: Depression is a common heterogeneous, debilitating and life-threatening mood disorder affecting different segments of the community. Several chemical and synthetic medicines as standard are being employed to treat depression and may lead to complete recovery in only 50% of clinically depressed patients but causes many adverse effects. Thus, scientists are increasing their interest in research towards the utility of medicinal plants for antidepressant activity. Several medicinal plants and its derived medicinal products have been reported to exert antidepressant action in different animal models by the combined effect of their phytoconstituents. In the brain, the alteration in level of various endogenous molecules like noradrenaline (NA), acetylcholine (Ach), serotonin (5-HT), dopamine, glucocorticoid, γ -aminobutyric acid (GABA), corticotrophin-releasing hormone (CRH) and hippocampal volume are responsible for depression. Therefore, most medicinal plants through synaptic regulation of serotonin, noradrenaline, and dopamine, overcome the altered level of monoamines in the brain and also reinforcing antioxidant defense mechanism, regulate hypothalamic-pituitary-adrenal axis activity and reducing inflammatory mediators. So, herbal medicines are widely used in contrast to allopathic or synthetic medicines globally because of their least side effects and wide therapeutic applications. The present review aims to highlight the medicinal plants and their antidepressant mechanism involved in the treatment of depression by animal model studies.

INTRODUCTION: In the present world, there is several life-threatening neurological disorders such as Alzheimer's, epilepsy, multiple sclerosis, Parkinson's disease, brain tumor, *etc.* Besides them, there are certain disorders such as mood swing, anxiety, and depression, which may not be life-threatening, but at the same time, degrade the quality of life.

One of the mood disorders, depression is an extensive medical condition which not only affect mental health but also have an impact on physical health resulting in feeling of sadness or emptiness, insomnia, alopecia, risk of heart attack, constricted blood vessels, uncontrollable thoughts of suicide, lower interest in sex, feeling of tiredness, trouble in taking decisions and weakened immune system *etc.*

According to World Health Organization (WHO) statistics, the depressive disorder is the third most disabling disorder worldwide, affecting 1% to 2% of teenagers and 0.9% to 42% of elderly patients in the European population. Over 36 percent of the worldwide population attempt suicide due to bipolar disorder or major depression.

QUICK RESPONSE CODE 	DOI: 10.13040/IJPSR.0975-8232.11(1).1-13
	The article can be accessed online on www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(1).1-13	

Depression is of various kinds' namely major depression, persistent depression, postpartum depression, psychotic depression, seasonal depression, and Bipolar disorder.

Persistent Depressive Disorder: It is also known by the name dysthymia, and such a depression lasts for a minimum of two years. The symptoms vary in severity, and their occurrence could sometimes be serious while at other times it may be less severe, but altogether if only the symptoms persist for two consecutive years, this could be characterized as a persistent depressive disorder.

Postpartum Depression: It is much more serious than the "Baby blues" experienced by perturbing mothers. The postpartum depression makes it very tough for the recent mothers to fulfill their childcare and also their own routinely activities due to their extreme emotions of anxiety, sorrow, and lassitude.

Psychotic Depression: This kind of depression is a combination of depression with any form of psychosis such as delusions, hallucinations, and even suicidal thoughts. People in such condition are most commonly found in delusions of poverty or illness.

Seasonal Affective Disorder: This can more easily be understood as winter depression as its onset is in winters due to lesser intensity of sunlight and thrusts during spring and summer. This kind of depression has symptoms like social withdrawal, more sleep, and weight gain.

Bipolar Disorder: Although, bipolar disorder is not a part of the depression, a person with bipolar disorder experience rise and fall in moods. The mood variation could be extremely irritable known to be mania and less intense as hypomania. These mood swings match the characteristics of depression and so included in the list of depressions.

Risk of Endogenous Bioactive Molecules for Depression: With the advancements in studies related to depression, researchers have established some new aspects to be considered in depression. These include an increased level of corticotropin-releasing hormone (CRH); increase in the level of gamma-aminobutyric acid (GABA); unrestricted

glucocorticoid activity in psychotic depression; elevation in acetylcholine activity; and loss in hippocampal volume. These outcomes lead to the development of newer hypothesis in the study regarding depressions.

1. Norepinephrine: Norepinephrine is a catecholamine which is synthesized from tyrosine. Norepinephrine is found in the brain, plasma, sympathetic nervous system, and heart tissues. The process of synthesis of norepinephrine is: tyrosine converts to L-dopa under the action of tyrosine hydroxylase and this L-dopa in the presence of dopa decarboxylase turns into dopamine which then finally converts into norepinephrine by the activity of dopamine beta-hydroxylase¹.

Norepinephrine is further translated into epinephrine in adrenal tissues via phenyl-n-methyltransferase². CNS do not have much specific role to play in the samples of norepinephrine collected from urine or plasma whereas there are previously established studies that showed 20-30% of 3-hydroxy-4-hydroxyphenyl glycol (MHPG) is obtained from brain³.

It has been reported that in depressed patients, specifically bipolar and the subgroup of unipolar depressives, their urinary MHPG levels were lesser when compared with healthy individuals. On assigning both bipolar and unipolar depressives into two groups each I and II, investigators reported a similar pattern of MHPG levels in both categories, *i.e.*, low MHPG levels were reported in group I than group II^{4,5}.

But there were some cases of unipolar patients that reported an increase in MHPG⁶ and urinary free cortisol levels⁷. The level of catecholamine and MHPG in cerebrospinal fluid (CSF), urine or plasma is always higher in cases of manic or euthymic bipolar patients in comparison to bipolar depression patients^{8,9}. Altogether, this previous study helped to understand the fact that norepinephrine levels play an etiological role in mood disorders. These data revealed that depression exists in two forms- a norepinephrine depression, marked by low levels of MHPG¹⁰ and another, a serotonin depression¹¹ marked by the high levels of MHPG.

Tyrosine Hydroxylase / Locus Coeruleus:

Tyrosine hydroxylase or locus coeruleus act as the nucleus of the Norepinephrine system in brain¹². The post-mortem studies of depressed patients or suicide¹³ casualties reported upregulated activity of tyrosine hydroxylase¹⁴ in brain pointing towards chronic stress. There were other studies which produced a contradictory report such as there were cases that reported a decrease in NE in neurons in suicidal victims¹⁵, whereas in other studies NE transporter sites were reduced, but NE level in neurons was sufficient in numbers¹⁶. When putting together, these studies concluded an alteration of NE in suicide victims but cannot produce any convincing pattern of NE alterations.

Norepinephrine and Adrenoceptor: The production and release of NE are regulated by presynaptic α_2 receptors by acting as thermostats. Studies have shown an elevated activity of α_2 in platelets of depressed patients¹⁷. The receptor activity of α_2 could be computed by monitoring the response of cAMP in regard with agonists since these receptors are bound to adenylate cyclase second messenger system in such a way that their agonist inhibits cAMP formation^{18, 19}. It has been documented that stimulation of postsynaptic α_2 adrenoceptor inhibits hypothalamic-pituitary-adrenal axis function²⁰; the abnormally increased cortisol response to yohimbine (indole alkaloid, α_2 -antagonist) suggests a relative sub sensitivity of postsynaptic α_2 adrenoceptor in depression¹⁸.

2. Serotonin: Serotonin or 5-hydroxytryptamine (5-HT), a monoamine neurotransmitter, have a significance role in appetite and mood **Fig. 1**. It is synthesized within the raphe from amino acid L-tryptophan in the brain, but it does not cross the blood-brain barrier by itself, but its metabolite 5-hydroxy indole acetic acid (5-HIAA) is present in a measurable amount in CSF.

Serotonin metabolism is regulated by monoamine oxidase (MAO). The interest to study about serotonin was established because low CSF 5-HIAA levels were found in hospitalized depressives (depressive patients) who have attempted suicide²¹ by violent methods such as hanging and also the antisocial personalities who have improper impulse control^{22, 23}. With recent advancements, a link between low serotonin level

and difficulties in impulse control have been established stating the suicidal nature of antisocial subjects if depressed²⁴.

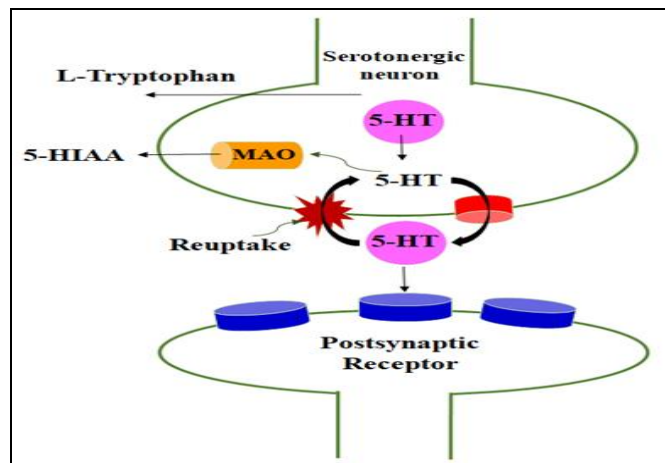


FIG. 1: CAUSES OF DEPRESSION DUE TO POST-SYNOPTICALLY INSUFFICIENT 5-HT

Serotonin and Serotonergic Receptors: There have been several 5-HT receptors (both presynaptic and postsynaptic) studied in depressed patients, among which 5-HT_{1A} and 5-HT_{2A} became the center of attraction. 5-HT_{2A} receptors are found post-synoptically in the frontal cortex and also in platelets^{25, 26}. Increased binding sites in suicidal patients have been reported²⁷, but they are not considered as diagnosis (diagnostic feature) for the cognitive aspect of major depression²⁸.

5-HT_{2A} receptors are part of phosphoinositide second messenger system. When this receptor is activated by agonists, phosphatidylinositol 4,5-bisphosphate get hydrolyzed to form diacylglycerol and 1, 4, 5-triphosphate in the presence of phospholipase C. This phosphoinositide system is studied in suicide victim's brain. It was reported that phorbol 13, 14-dibutyrate binding with protein kinase C (activated by diacylglycerol) in the prefrontal cortex was lesser in teenage suicide victims²⁹, also decrease in the levels of beta-1 isozyme was found³⁰. On studying number and activity of 5-HT_{1A} receptors in post-mortem brain, it was found that in some cases there was an increase in 5-HT_{1A} Bmax in non-violent suicide victims while in some other suicide victims the cases failed to establish any difference in 5-HT_{1A} receptors activity³¹.

3. Dopamine: Although, dopamine is a precursor of NE and is also widely present in the brain, but

still NE remains the center in the etiologic study of depression. The levels of CSF DA are reported to increase in depressive patients³², but levels of CSA homo-vanillic acid (HVA), which is a metabolite of CSF DA decreased^{32, 33}. DOPAC levels linked with suicidal nature of depressives were found to decrease when compared with controls^{34, 35}. Increased levels of CSF HVA and CSF DA are found in an association with symptoms of psychotics, agitation in major depression, and delusional depression. Data collected from preclinical studies have shown that DA activities and metabolism in some particular brain parts could be altered by HPA axis activity^{36, 37}.

4. GABA (Gamma-Amino Butyric Acid): GABA has become a topic of interest, due to the wide use of anticonvulsants in mood disorders. It is an inhibitory neurotransmitter which regulates activities of both norepinephrine and dopamine and also balances the threshold of seizures. GABA receptors are categorized into forms GABA_A and GABA_B, which are associated with chloride channels and calcium channels, respectively. GABA_B receptors present in the frontal cortex are upregulated by antidepressants and mood stabilizers in case of the rat.

These GABA_B agonists mark an increase in cAMP response to norepinephrine and also a decrease in β -adrenergic response to TCA. The low levels of plasma GABA^{38, 39, 40}.

5. Neuroendocrine Systems: The neuroendocrine system was initially considered for investigating activities of neurotransmitters like norepinephrine and serotonin, in cases of depression but with the time the focus has diverted to investigate the roles played by the axes in the pathogenesis of diseases. The three axes to be focused in cases of major depression includes HPA, HPT, and HGH **Fig. 2**.

Hypothalamic-Pituitary-Adrenal (HPA) Axis: There is several evidence that points towards abnormalities in HPA Axis during the depression. An increase in both serum cortisol and their precursor's level was observed in depressive patients^{41, 42} especially during the evening and overnight¹⁰, when the axis is supposed to be dormant and is also believed to cause suicidal ideations³⁷. The levels of cortisol are high

throughout day and night in patients with severe depression conditions or in cases of major depression, which also indicates a very high-stress level of patients¹⁰.

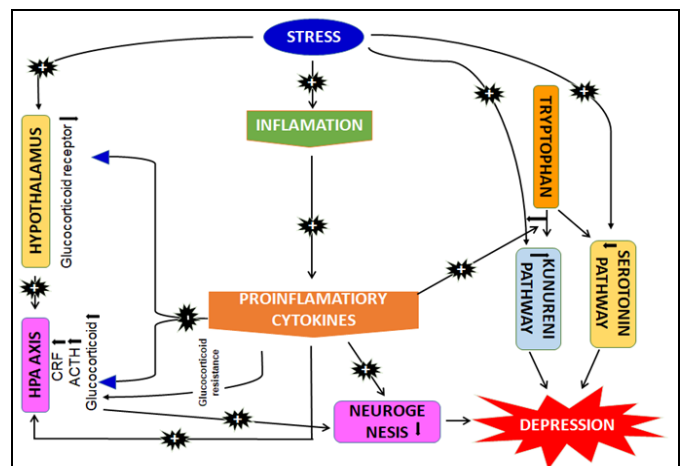


FIG. 2: ROLE OF NEUROIMMUNE AND NEUROENDOCRINE SYSTEM IN DEPRESSION. ('+' ACTIVATE, '-' INHIBIT)

A study conducted based on types of patients revealed that outpatients with mild and nonpsychotic disorders showed lesser cases of non-suppression and were also at a lesser risk for relapse when compared with psychotically depressed patients. Studies have shown that in depressed patients' level of corticotrophic releasing hormone (CRH) in CSF or plasma remains high due to their blunt responses to adrenocorticotrophic hormone (ACTH)^{43, 44}. Imaging techniques have shown that the size of pituitary⁴⁵ and adrenal gland⁴⁶ increases during the depression, and it reduces to normal with the recovery of patient⁴⁶.

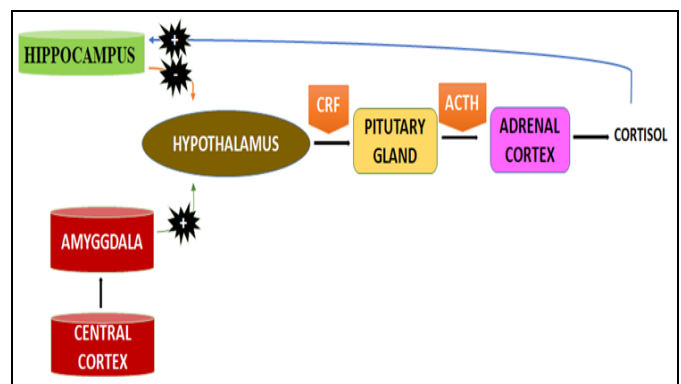


FIG. 3: FEEDBACK MECHANISM OF NEURAL CIRCULATORY SYSTEM OF HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS. ('+' ACTIVATE, '-' INHIBIT)

In suicide victims' number of arginine vasopressin (AVP) neurons and serum AVP is increased, which

also became a cause for increasing CRH stimulation of ACTH⁴⁷⁻⁴⁹. Besides hypothalamus CRH is also present in extrahypothalamic region such as amygdala where it has a particular role to play in fear responses and if it gets over activated, it leads to panic and depressions^{50, 51}. Low levels of ACTH are also found in patients of atypical depression and post-traumatic stress disorder (burn out syndromes) **Fig. 3**. The data proves that, HPA axis over activity and under activity both accounts for various depressive subtypes⁵².

Hypothalamic-Pituitary- Thyroid (HPT) Axis:

The major reason for considering the hypothalamic-pituitary-thyroid (HPT) axis is the overlapping of major depression symptoms with hypothyroidism⁵³. In studies conducted on depressives, an elevation in CSF thyrotropin-releasing hormone (TRH) was reported which should be followed by blunted thyroid-stimulating hormone (TSH) response⁵⁴ as the TRH levels of pituitary remained low, and this was experienced in around 25% of cases of major depression⁵⁵. The depressed patients were diagnosed with type III and type IV subclinical hypothyroidism which is characterized by normal level of T3, T4, and TSH but are observed by elevated responses of TSH to TRH and also the presence of antithyroid antibodies^{53, 55}.

These data have led to a conclusion that patients with symptomless autoimmune thyroiditis and positive antibodies are reported to be depressive patients⁵⁶. Some data revealed elevation in both central TRH activity and subtle forms of hypothyroidism (suggestive of low T3 and TRH activity) has a significant potential role in major depression⁵⁵.

Human Growth Hormone (HGH): Growth hormone is synthesized in the anterior pituitary and regulated by growth hormone-releasing factor (GRF) which stimulates the release of GH and somatostatin, which inhibits its release. Somatostatin is also considered as a neurotransmitter and is found in extra-hypothalamic regions, and it is known that all major neurotransmitters involved in mood disorders affect growth hormone release⁵⁷. Nocturnal growth hormone levels increase in depression, while daylight-stimulated growth

hormone levels increase in both unipolar and bipolar depressions⁵⁸. Growth hormone response to GRF has blunted in depression⁵⁹, and also the CSF levels of somatostatins are low in cases of depression⁶⁰.

6. Homocysteine: Elevated level of plasma homocysteine (>15mcmol/L) may lead to major depressive disorder. Several studies have documented the evidence for the association between elevated level of homocysteine and depression⁶¹. It is relevant to notice that folate deficiency was observed in up to one-third of patients with severe depression unlike of their ages, but this topic also has a conflicting result, due to the fact that most studies evaluating homocysteine levels are performed in elderly patients and there is an increase in both homocysteine levels and depression onset with aging.

The folate deficiency being primary or secondary to depression makes no difference, since its low level are meant to limit the response to antidepressants. There are a number of studies that supports the efficacy of folate replacement therapy in improving mental state recovery and showed antidepressant function of s-adenosyl methionine, probably via the one-carbon metabolism pathway which produces methyl groups required for the synthesis of serotonin⁶², dopamine, and norepinephrine which imbalance in the patients with depression and psychiatric disorder⁶³.

Phytochemicals against Depression: Besides, autoimmune and cardiovascular diseases phytochemicals derived from herbs also help to reduce the risk of neurodegenerative disease. Polyphenols such as curcumin, ferulic acid, and resveratrol are known to possess anti-inflammatory and antioxidant properties, but they have also known to show neuroprotective effects in symptoms of depression.

Carvacrol: Carvacrol is a monoterpene phenol obtained from oregano and thyme and is known for its anti-inflammatory, analgesic, antiarthritic, anti-allergic, anticarcinogenic, antidiabetic, cardio-protective, gastroprotective, hepatoprotective, and neuroprotective properties⁶⁴.

Dong *et al.*, showed that when carvacrol is co-administered with compounds that undergo

CYP2A6-mediated metabolism⁶⁵ in oral dose (12.5-50mg/kg) induced anti-depressant effect that was regulated by a dopaminergic pathway in mice⁶⁶. Oral administration of carvacrol was reported to produce a raise in 5-HT and dopamine in hippocampus and prefrontal cortex⁶⁷.

Curcumin: The major active constituent of *Curcuma longa* is curcumin, which is a yellow colored natural phenol widely known as Oriental medicine since historical time, but nowadays its medicinal potential is under study. It has been reported that curcumin supplements have shown antidepressant potential in improving damage caused in behavioral abnormalities in open field and passive step-down avoidance in depressant models⁶⁸.

Also, a decrease in immobility time in forced swimming test and improvement of bilateral olfactory bulbectomy-induced alteration of 5-HT, noradrenaline, and dopamine in hippocampus were also observed when treated with curcumin. Kulkarni *et al.*, came to a conclusion that curcumin elevated 5-HT levels in mice and when co-administered with other antidepressants like fluoxetine, venlafaxine, and bupropion, it produced synergistic effects⁶⁹.

Curcumin has also been reported to rehabilitate the biochemical and behavioral changes occurred due to chronic stress⁶⁹. Antidepressant activity of curcumin could be related to the elevation of hippocampal brain-derived neurotrophic factors which are deeply indicated in the pathophysiology of depression^{70,71}.

Ferulic Acid: It is a phytochemical that is known for its anti-inflammatory⁷², anti-tumour⁷³, anti-diabetic⁷⁴, neuroprotective⁷⁵, and anti-oxidant⁷⁶ properties. Oral administration of ferulic acid reduced stress-induced abnormal behaviors in mouse depression model and also increased phosphorylation of CREB and brain-derived neurotrophic factor mRNA hippocampal levels^{71,77}.

Quercetin: Quercetin is a non-specific protein kinase enzyme inhibitor that is known to inhibit depression-like behaviors occurring due to the over activity of the hypothalamic-pituitary-adrenal (HPA) axis in mice^{71,78}.

Resveratrol: Resveratrol is a natural phenol found widely in grapes and red wine. Trans-resveratrol is found to show antidepressant activity due to its interaction with the monoaminergic system by increasing levels of 5-HT/noradrenaline in mouse brain. Resveratrol is capable of inhibiting chronic stress-induced depression-like behavior^{71,79}.

Yohimbine: Yohimbine is an indoloquinolizidine alkaloid derived from the bark of African tree *Pausinystalia johimbe*. Despite parallel MHPG response in control and depressed patients, the response to yohimbine was significantly greater in depressed patients than in controls. Since there is evidence that stimulation of postsynaptic alpha 2-adrenergic receptors inhibit HPA axis function and the abnormally increased cortisol response to the alpha 2-antagonist yohimbine suggests a relative sub-sensitivity of postsynaptic alpha 2-adrenergic receptors in depression¹⁸.

Pharmacological Impact of Antidepressant Action of Medicinal Herbs:

***Aloysia polystachya*:** The hydroalcoholic extracts of leaves of *Aloysia polystachya* at various doses produce antidepressant activity in Forced Swim Test (FST) conducted on female rats. Its antidepressant property is due to the presence of bioactive constituents such as thujone and carjone⁸⁰.

***Aloysia triphylla*:** *Aloysia triphylla* belongs to family Verbenaceae. Two active constituent hesperidin and artemitin are known to show therapeutic activities such as anti-inflammatory actions, anti-oxidant properties, and also tonic effect upon nervous system such as in rescuing from depression⁸¹.

***Aniba riparia*:** *Aniba riparia* belonging to family Lauraceae is found to possess antidepressant activity at various doses due to the presence of riparin III in tail suspension test and forced swim test conducted on mice⁶⁶.

***Bacopa monnieri*:** Brahmi is found to reduce depression score in demented and non-demented elders due to the presence of saponins like bacopasides VI-VIII, bacopaside I and II and bacopasaponin C. Its ability to treat neurodegenerative disease was taken into

consideration due to its nootropic and cholinergic property^{82,83}.

Berberis aristate: Daruhaldi is known to show anti-depressant activity in forced swim test conducted on mice by enhancing brain serotonin, noradrenaline, and dopamine levels. All this is believed to be due to the presence of an isoquinoline berberine⁸⁴.

Camellia sinensis: The aqueous extract of leaves of *Camellia sinensis* is found to show anti-depressant like activity in male mice during forced swim test⁸⁵.

Cinnamomum verum: Cinnamon, a plant from Lauraceae family, is known to possess anti-depressant, anti-viral, anti-microbial and anti-oxidant properties. The major constituents that contribute to these therapeutic activities are cinnamaldehyde⁸⁶ and proanthocyanidins⁷¹.

Citrus aurantium: The studies have reported that essential oils of *Citrus aurantium* could be considered as the choice of treatment for depression over the chemical drugs due to the positive and no side effects produced in depression cases⁸⁷.

Echium amoneum: The petals of *Echium amoneum* contains phenolic compounds such as sanding, defending, and rosmarinic acid that is reported to show anti-depressant, analgesics, anti-oxidant, and anti-bacterial properties⁸⁸.

Hippophae salicifolia: This medicinal herb is known from early times as a potent prophylactic and health promotive agent. Its bioactive contents such as ellagic acid, vitamin C, and coumarins are known to provide neuroprotective properties such as anti-depressant activity, control of appetite, sleep, memory, and learning⁸⁹.

Hypericum perforatum: St. John's Wort is a medicinal plant well known for its anti-depressant property. Its extract, named as WS 5570, is in markets of Germany applied in acute term treatment of mild to moderate major depression. The actual mechanism of *Hypericum perforatum* remains unknown, but their *in-vitro* and *in-vivo* studies have demonstrated that they act by elevating brain serotonin levels, upregulation of 5-

HT2 receptors and by inhibition of serotonin reuptake^{90,91}.

Lavandula angustifolia: Lavender essential oil is well known for its aromatherapy as a relaxant, but the inhalation of its major constituent linalool is also known to possess anti-depressant, anxiolytic, and anti-conflict effects⁹².

Melissa officinalis: In Iranian folk medicine, the Lemon balm is used for treating nervousness, lack of energy, and depression in young girls. The major constituents of lemon balm are citronellal, geranial, citral, rosmarinic acid, flavoglycoside acids and three terpenes⁹³.

Morinda officinalis: The ethanolic extract of *Morinda officinalis* shows anti-depressant activity by upregulating serotonin levels in rodent models of depression in learned helplessness test and forced swim test⁹⁴.

Nyctanthes arbortristis: The hydroalcoholic leaf extract of night Jasmine is found to demonstrate anti-depressant activity in depression models of rodents in forced swim test and learned helplessness test^{95,96}.

Ocimum sanctum: Tulsi, the sacred herb is blessed with the number of therapeutic properties, and a recent study concluded that its root extract had shown anti-depressant activity in mice when tested in forced swim test and tail suspension Test.

The dopamine and serotonin systems are believed to be involved in the anti-depressant property of tulsi^{97,98}.

Oenothera biennis: The seeds of *Oenothera biennis* are employed in the production of evening Primrose oil. This oil has shown considerable anti-depressant property in a rodent model of Chronic Fatigue Syndrome⁹⁹.

Salix aegyptiaca: In Iranian folk medicine, musk willow plant flower is of great therapeutic importance. Each plant possesses single-sex *i.e.*; the plant is either male or female. The distillates of male flowers of the plant are used in the treatment of depression, anemia, vertigo, and various cardiovascular diseases¹⁰⁰.

Tinospora cordifolia: The dried stem extract of *Tinospora cordifolia* demonstrated anti-depressant activity in anti-depressant models such as tail suspension test and forced swim test with the involvement of monoaminergic and GABAergic system¹⁰¹.

Valeriana officinalis: The root extract of *Valeriana officinalis* showed anti-depressant, anxiolytic, and sedative properties due to the presence of active constituents such as valenol, valepotriates, and baldrinals valerenic¹⁰².

Viola odorata: Sweet violet is the herbal plant of Iranian folk medicine belonging to the family Violaceae whose flower is useful in treating depression, sleeping disorders, and as a blood pressure-lowering agent¹⁰³.

Withania somnifera: *W. somnifera* also known as Indian ginseng belonging to the family Solanaceae is found to show anti-depressant effect by targeting serotonergic system in rodent behavior test studies such as open field test, forced swim test, tail suspension test and learned helplessness test¹⁰⁴⁻¹⁰⁸.

Zingiber officinale: Other than the established uses of ginger, a recent study showed that hydro-alcoholic extract of rhizome of ginger when administered orally caused depletion in immobility period of rats in forced swim test and tail suspension test hence leading to the conclusion that they possess anti-depressant properties^{109, 110}.

Some other plants have antidepressant activity showed in **Table 1**.

TABLE 1: APPLICATION OF MEDICINAL PLANTS IN TREATMENT OF DEPRESSION

Plant & Family	Part use & Extract	Dose	Model/ Patients	Study design	Effects and mechanisms
<i>Camellia sinensis</i> , Theaceae	Leaf, Aqueous	5, 10, and 20 mg/kg	Mouse behavioral models of depression & HPA axis	Mice, Oral adm. (administration)	In tail suspension test reduce immobility and regulate HPA axis in forced swimming test ⁸⁵
<i>Piper methysticum</i> , Piperaceae	Root, Aqueous	16 g containing 250 mg of kavalactones/day	Patient with Depression	RCT (Randomized controlled trials)	Significantly decrease the Montgomery-Asberg Depression score and anxiety inventory with no severe adverse effects and no clinical liver toxicity ¹¹²
<i>Rhodiola rosea</i> , Crassulaceae	Root, Alcoholic	1.5–6 g/kg	Cerebral hippocampus of depressive rats induced by Chronic Mild Stress	Rats, Oral adm.	Augment hippocampus 5-HT level-stimulated propagation of neural stem cell, reconstructing the injured neuronal cells in hippocampus ¹¹³
<i>Echium amoenum</i> , Boraginaceae	Flower, Aqueous	375 mg/day	Patient with psychotic symptoms	RCT design	At four weeks of a study Enhance the Hamilton Rating score for Depression; however this result was not maintained at 6 weeks ¹¹⁴
<i>Hypericum perforatum</i> , Clusiaceae	Herb, hydro-alcoholic	0.1 and 0.2 g/kg	Diabetic induce depression and anxiety rat model	Rats, peroral adm.	Significantly exhibit anxiolytic activity in elevated plus maze (EPM) test and open-field exploration test (OFT) ¹¹⁵
<i>Crocus sativus</i> , Iridaceae	Flower, Aqueous	0.03 g/day	Patient with a mental disorder	RCT design	For depression, promote Hamilton Rating Score ¹¹⁶
<i>Lavandula angustifolia</i> , Lamiaceae	Flower, hydro-distillation	Lavender aromatherapy (200µl)	Scopolamine induced spatial memory impairment in rats	Rats, Inhalation	Prevent depression-like demeanor in forced swimming and elevated plus-maze tests. Inverse Spatial memory deficits ¹¹⁷
<i>Nelumbo nucifera</i> , Nymphaeaceae	Fruit, methanolic	4 g/kg	Sucrose intake model	Rats, Oral adm.	Inverse reduced sucrose intake and the reduced 5-HT1A receptor binding in brain ¹¹⁸
		2.1 g/kg	Forced swimming test	Rats, Oral adm.	In the forced swimming test (FST), enhance strive time and first latency period ¹¹⁹
		Rats 0-2.0 g/kg for, Beagle Dogs 0-4.0 g/kg	Chronic mild stress model and FST	Oral adm. in rats or beagle dogs	In forced swimming test (FST), reduced the start latency, grooming time, rearing number, and reduced visiting counts created by chronic mild stress. No toxicity up to 28 days of adm. in dogs and 13 weeks of administration in rats ¹²⁰

CONCLUSION: The new concept of looking for drugs from natural sources has been put to use as an anti-depressant and has gained world-wide interest during the last decades. Such advancement in the world of pharmaceuticals will be of great fortune for developing nations. This review enlists certain medicinal plants that could be positively included in anti-depressant therapy. Medicinal plants and their active constituents can be associated with decreasing risk of depressive disorders.

Active constituents like carvacrol, curcumin, ferulic acid, quercetin, and yohimbine obtained from plant sources are considered to be potent antidepressants. The world needs to shift itself towards the drugs obtained from natural sources to avoid expensive synthetic medicine as well as the side effects like insomnia due to reboxetine, seizures due to amoxapine, G.I. Distress due to paroxetine *etc.* experienced due to intake of synthetic anti-depressants.

The easier availability, lesser side effects, and cost-effectiveness of drugs obtained from medicinal plants make them more desirable therapeutic agents. The outcome of the study is an aid to recognize and choose effective and safer approaches in the treatment of depression. The need of the hour is to clinically investigate and precisely calculate the role played by these medicinal plants in cure and management of depression¹²¹⁻¹²².

ACKNOWLEDGEMENT: The author, thanks GLA University, for providing the necessary facility to accomplish the work.

CONFLICTS OF INTEREST: The author(s) confirm that this article content has no conflict of interest.

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How to cite this article:

Gupta J, Gupta R and Varshney KK: Emerging mechanisms and potential antidepressant action of medicinal plants. *Int J Pharm Sci & Res* 2020; 11(1): 1-13. doi: 10.13040/IJPSR.0975-8232.11(1).1-13.

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