REVIEW ARTICLE

ISSN: 2455-8095
doi: https://doi.org/10.21477/ijapsr.9.1.01

The Role of Natural Extracts in Depression: Modulating Neurotransmitters for Antidepressant Effects

Valaboju Swetha[1], Vallapu Nandini[1], Vasudev Pareek[1], Verpula Uday Kumar[1], Volavuthu Srihari[1], Kondapuram Devi[2*]

[1]Department of Pharmacology, TKR College of Pharmacy, Medbowli, Meerpet, Balapur, Hyderabad, Rangareddy, Telangana, 5000097.

[2]Department of Pharmacology, TKR College of Pharmacy, Medbowli, Meerpet, Balapur, Hyderabad, Rangareddy, Telangana, 5000097.

ABSTRACT

Objective: This study explores the neurobiological underpinnings of Major depressive disorder (MDD), focusing on neuroimaging, neurotransmitter dysregulation, and emerging therapeutic approaches, to identify potential avenues for innovative treatment development.

Methods: A review of recent neuroimaging studies, postmortem analyses, and neurotransmitter research was conducted to synthesize findings on structural and functional brain changes in MDD. The monoamine, glutamate, and GABAergic theories of depression were evaluated alongside emerging evidence for plant-derived therapeutics.

Results: Neuroimaging reveals structural brain changes in MDD, including reduced brain volumes, enlarged lateral ventricles, and white matter microstructural deficits suggestive of myelin sheath loss. Postmortem studies report altered neuronal and glial density, as well as synaptic gene expression. Dysregulation of neurotransmitters—Gamma-amino butyric acid (GABA), glutamate, serotonin, dopamine, and norepinephrine—impairs synaptic communication, contributing to mood disturbances. While the monoamine theory attributes depressive symptoms to neurotransmitter deficiencies, recent findings highlight the roles of glutamate dysregulation and GABAergic deficits. Notably, plant extracts demonstrate antidepressant potential by modulating neurotransmitter levels and influencing the GABAergic system.

Conclusion: Advances in understanding the pathophysiology of MDD underscore the need to target specific neurotransmitter systems. Emerging evidence supports the development of innovative treatments, including plant-based interventions, to address the limitations of current therapies and improve patient outcomes.

Keywords: Depression, neurotransmitters, serotonin, dopamine, norepinephrine, gamma-amino butyric acid (GABA), glutamate.

1. INTRODUCTION

A staggering 12% of people worldwide suffer from major depressive disorder (MDD), a potentially debilitating mental illness that is most prevalent in the US among women, young adults, and the elderly. Studies anticipate a substantial rise in MDD patients globally after the COVID-19 pandemic, adding to the enormous burden this condition already has on public health systems.[1]

A diagnosis of major depressive disorder (MDD) is made when a person has a persistently low mood for at least two weeks, accompanied by additional symptoms such as changes in appetite, weight, and energy levels.[2] Antidepressant medication is often recommended, although first-line therapy fails to achieve remission in around half of the patients.[3] Because of this, a better knowledge of the pathophysiology of MDD is necessary for the creation of more effective therapies.

Neuroimaging research has recently shown that people with MDD have altered brain structure and function. There are several symptoms that may be seen, such as smaller brain volumes, larger lateral ventricles, and changes in the microstructure of white matter that might indicate a loss of myelin sheath.[4,5] Concurrently, alterations in neuronal and glial density and size, as well as decreased expression of pre- and postsynaptic genes,

Corresponding author
Kondapuram Devi
Email : devikondapuram87@gmail.com

Received: 05-11-2023 **Accepted:** 25-12-2023 **Available Online:** 01-01-2024

have been shown in postmortem investigations of brain regions in several patients.[6]

1.1. Role of neurotransmitters in depression

In the intricate process of neurotransmission, chemical messengers called neurotransmitters allow neurons to communicate with one another. Key neurotransmitters such as GABA, glutamate, serotonin, dopamine, and norepinephrine are dysregulated in depression, which impairs normal synaptic communication. To trigger either an excitatory or inhibitory reaction, these neurotransmitters are discharged into the synaptic cleft by presynaptic neurons and then bind to certain receptors on postsynaptic neurons (Figure 1). Disruptions to this mechanism may cause the mood abnormalities associated with depression, which is why its proper regulation is critical for emotional stability.

1.1.1. Monoamine Hypothesis

Over 30 years ago, the monoamine theory of depression was put forward, which states that manic episodes are associated with an overabundance of norepinephrine (NE), serotonin (5-HT), and dopamine (DA) in the brain and that depression is the consequence of a deficit of these neurotransmitters.[7] The discovery that the medication reserpine, which depletes presynaptic reserves of NE, 5-HT, and DA, generates symptoms similar to depression lends credence to this notion. Iproniazid, on the other hand, was originally designed for TB but, by blocking monoamine oxidase (MAO), it increased levels of 5-HT and other neurotransmitters in the brain, which may cause euphoria and hyperactivity in some individuals. Alterations to the production, release, or receptor sensitivity of these neurotransmitters may amplify the symptoms of manic and depressive episodes because of the impact they have on mood, motivation, and behavior.

By removing neurotransmitters from the synaptic cleft and therefore ending their effects on pre- and postsynaptic receptors, transport proteins play a crucial role in monoaminergic transmission. The 5-HT transporter may be studied in vivo in many forms of depression since it is found in both human platelets and the central nervous system (CNS).[8] Major depressive disorder is unique among mental illnesses in that studies using tagged proteins and 5-HT uptake assays in platelets have repeatedly shown impaired transporter function.[9] Problems with subject selection and protein breakdown

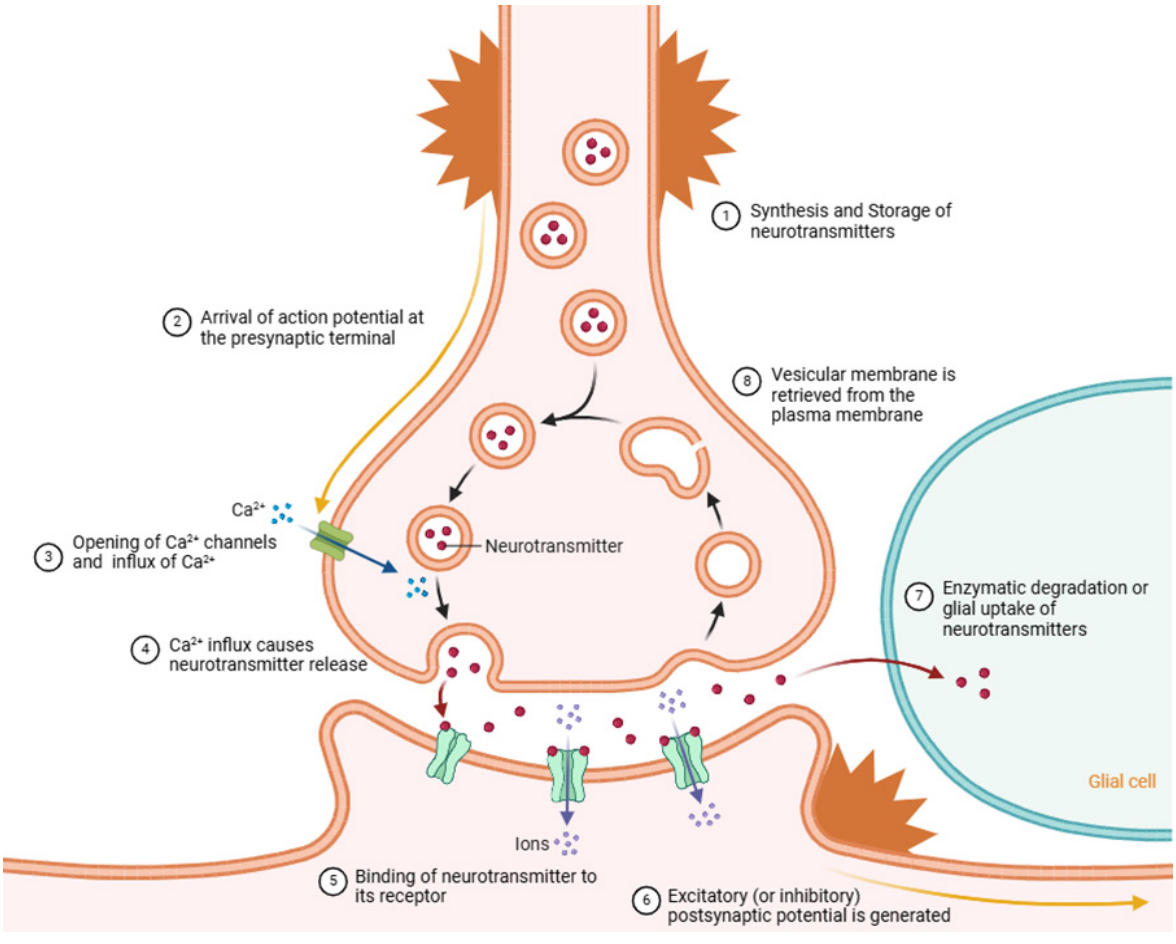

Figure 1: Steps involved in neurotransmission

after death may explain why findings from postmortem brain samples are less consistent.[10]

Problems with neurotransmission may arise from alterations in receptor function, such as a lack of monoamines or an interruption in the downstream signal transmission, or from changes in the coupling between transmitters and receptors. According to Lin et al.,[11] there are several receptor subtypes in both the noradrenergic and serotonergic systems. While α- and β-adrenoceptors control the transmission of NE, 5-HT acts on many receptor classes, ranging from 5-HT1 to 5-HT7, with numerous subtypes in each.

Changes in variables like neurotransmitter concentrations may cause receptors to be up- or downregulated. There has been a lot of research; however, the results on whether or not untreated depression affects the number or affinity of monoamine receptors are mixed. Some notable discoveries include an increase in sensitivity of presynaptic α2-adrenoceptors, which control the release of norepinephrine, and changes in the quantities and specificities of 5-HT1 and 5-HT2 receptors in both the brain and platelets.[12] Distribution of various monoamine neurotransmitters in brain is illustrated in Figure 2.

1.1.2. *Glutamate Hypothesis*

According to the glutamatergic theory of depression, which is supported by research showing that N-methyl-D-aspartate (NMDA) receptor antagonists have antidepressant benefits,[13,14] higher glutamate levels are associated with depressive symptoms. A possible cause of long-term potentiation and depression is the activation of NMDA receptors by glutamate, which leads to excitatory neurotransmission and the influx of calcium ions (Ca^{2+}).[15,16]

The findings of studies investigating glutamate levels in depression have been contradictory. Both postmortem and proton magnetic resonance spectroscopy investigations have shown that individuals with major depressive disorder (MDD) had raised glutamate levels in their frontal and occipital brains, respectively.[17,18] Medial prefrontal cortex (PFC) glutamine-plus-glutamate levels were lower in depressive patients compared to healthy individuals in a meta-analysis of magneto-resonance spectroscopy (MRS) investigations,[19] but no such changes were detected in the dorsolateral PFC or medial temporal brain. According to Kantrowitz et al.,[20] a different meta-analysis indicated that the anterior cingulate cortex of depressed individuals had lower glutamate levels than healthy controls. Glutamate changes linked to depression exhibit geographical variances and inconsistencies, as shown by these results.

1.1.3. *GABAergic Hypothesis*

The GABAergic deficit theory proposes that major depressive disorder (MDD) is caused by poor GABAergic neuronal inhibition and that antidepressants may work by restoring GABAergic neurotransmission.[21] Supporting this theory are findings such as decreased concentrations of GABA in plasma, brain tissue, and cerebrospinal fluid (CSF), changes in the expression and subunit makeup of GABAA receptors, and decreased concentrations of neuroactive steroids (NAS) in CSF from depressed patients.[22]

Further evidence for this theory comes from neuroimaging investigations, postmortem cytology, and large-scale genome-wide association studies. Key neuroimaging results in MDD are consistently associated with downregulated genetic markers for astrocytes and cortical somatostatin-expressing GABAergic interneurons, according to these methods.[23] Brain areas associated with subgenual anterior cingulate, medial PFC, anterior insula, and aberrant connections in depression, as well as cortical thinning, have the highest expression of polygenic markers for somatostatin interneurons. Another finding is that anatomical abnormalities in the cortex of people with MDD relative to healthy controls are inversely

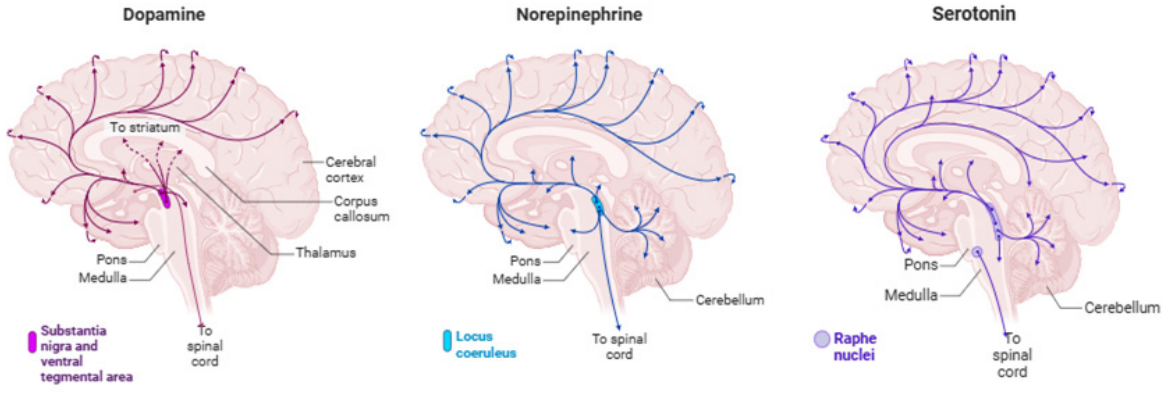

Figure 2: Distribution of Monoamine neurotransmitters

associated with the expression of the somatostatin gene marker SST.[24]

Both bipolar disorder and postpartum depression (PPD) have been linked to impaired GABAergic signaling.[25,26] These results highlight the possibility of therapeutic intervention by targeting GABAergic systems and the significance of GABAergic disruption in the pathogenesis of mood disorders.

1.2. Plant Extracts as Antidepressants: A Neurotransmitter-Centric Approach

There has been a lot of interest in exploring natural extracts to modulate neurotransmitters, especially using phytochemicals produced from plants as possible substitutes for synthetic medications. Inhibiting the actions of neurotransmitters including GABA, glutamate, serotonin, dopamine, and norepinephrine, these all-natural substances provide a potential way to alleviate symptoms of depression. This approach exemplifies the promise of plant-based therapies as a safe and effective treatment for depression.

1.2.1. Modulation of serotonin levels in depression

The serotonin system has been the target of many plant extracts that have shown encouraging antidepressant potential (Table 1). An inhibitory effect on serotonin reuptake may be possible due to the high binding affinities of extracts from *Callistemon citrinus* for the SERT.[27] Another study found that *Osmanthus fragrans* var. thunbergii floral ethanolic extract raised brain serotonin levels and had antidepressant-like effects in rats.[28] By increasing serotonin levels and upregulating serotonin receptors, the *Aegle marmelos* leaf extract considerably ameliorated depressive-like behaviors in rats modeled by chronic unpredictable mild stress (CUMS).[29] Another study found that the extract of *Lippia citriodora* increased the expression of serotonin receptors, which led to feelings of calm and antidepressant benefits.[30] Additionally, it was shown that *Nicotiana tabacum*, *Carica papaya*, and *Cannabis sativa* may enhance serotonin production by activating Cyclic adenosine monophosphate response element-binding protein (CREB), which lends credence to their antidepressant properties.[31]

The capacity to modify serotonin availability via distinct pathways has been shown by other prominent extracts as well. By inhibiting serotonin reuptake, an extract from *Platycladus orientalis* seeds (S4) increased serotonin levels in the prefrontal cortex and dorsal raphe nuclei.[32] *Vaccinium bracteatum* leaf extract was shown to have effects that were associated with regulating the hypothalamic-pituitary-adrenal axis, serotonin turnover, as well as the phosphorylation of Extracellular signal-regulated kinase (ERK)/Akt pathways.[33] While extracts from *Nardostachys jatamansi* and *Garcinia cambogia* both modulated serotonin transporter activity, the former showed antidepressant effects,[34] while the latter reduced anxiety and sociability problems in mice.[35] Furthermore, Lax et al.[36] found that *Mimosa pudica* and Leptolyngbya, an extract from cyanobacteria, were associated with the modulation of serotonin. Leptolyngbya modulated behaviors similar to depression by targeting the 5-HT7 receptor.

More research confirms that extracts that target the serotonergic system have antidepressant effects. A study conducted by Kukuia et al.[37] found that an extract from *Mallotus oppositifolius* raised serotonin levels in the prefrontal cortex, which in turn improved the density of dendritic spines, which are essential for synaptic plasticity and cognitive functioning. Oligosaccharides from *Morinda officinalis* increased serotonin synthesis by modulating the gut microbiota and facilitating 5-hydroxytryptophan (5-HTP) production.[38] A study conducted by Wu et al.[39] found that an extract from the bark of the *Eucommia ulmoides* tree, which is high in chlorogenic acid, increased the expression of Synapsin I and the release of serotonin. A study conducted by Kim et al.[40] indicated that *Fraxinus rhynchophylla* had a notable impact on serotonin levels in a chronic stress rat model. Similarly, Wusiman et al.[41] discovered that *Cordia dichotoma* fruit extract mitigated depressive-like behaviors via modulation of serotonergic neurotransmission. The mesembrine-rich extract of *Sceletium tortuosum* inhibited serotonin reuptake and considerably reduced depressive-like behaviors.[42] This study provides new hope for the development of plant-based antidepressants by illuminating the several pathways by which plant extracts regulate serotonin production, release, reuptake, and receptor activation.

1.2.2. Modulation of Dopamine levels in depression

Extraction from several plants has shown promise as a natural antidepressant because of its capacity to alter brain dopamine levels. Studies show that different plant extracts have different ways to affect dopamine levels, including via inhibiting MAO, blocking dopamine reuptake, activating dopamine receptors, and interacting with the cannabinoid system (Table 2). By blocking the enzyme MAO, which is responsible for the breakdown of dopamine, the extracts of *Nicotiana tabacum*, *Carica papaya*, and *Cannabis sativa* enhance the availability of dopamine (Fasakin et al., 2022).[31] These extracts may help alleviate depression symptoms by increasing synaptic dopamine levels and reducing dopamine breakdown. Similarly, Manikkoth et al.[52] discovered that alcohol-induced anxiety in Wistar albino rats may be modulated

Table 1: Plants modulating serotonin levels to treat depression

Extract	*Animal model*	*Dose*	*Mechanism*	*Reference*
Callistemon citrinus	Albino mice (20-30 grams)	100 and 200 mg/kg	The serotonin transporter is strongly bound to its molecules, which inhibits serotonin reuptake.	27
Osmanthus fragrans	-	-	Modulation of the serotonin system	28
Aegle marmelos leaf	Chronic unpredictable mild stress (CUMS)-induced model	150 mg/kg and 300 mg/kg administered orally	Boosted serotonin levels and receptor expression	29
Lippia citriodora		100 mg/kg	Modulation of serotonin receptors	30
Cannabis sativa, Nicotiana tabacum, and Carica papaya	Male Wistar rats	5, 50, 500, and 2000 mg/kg administered orally for 90 days	Elevated levels of serotonin produced by an upregulated route triggered by CREB activation	31
Platycladus orientalis seed	CUMS model	-	Elevate serotonin levels in the dorsal raphe nucleus and prefrontal cortex.	32
Vaccinium bracteatum leaf	Mice subjected to chronic restraint stress (CRS)	100 and 200 mg/kg administered orally	Reduce serotonin turnover	33
Nardostachys jatamansi	CUMS rats	-	Controlling the serotonin transporter	34
Leptolyngbya extract	Mice	-	Affects serotonin receptors, particularly the 5-HT7 receptor	36
Mallotus oppositifolius	Mice subjected to para-chlorophenylalanine (pcpa)-induced aggression	-	Reduces the effects of para-chlorophenylalanine, an agent that inhibits the production of serotonin,	37
Morinda officinalis	Mice subjected to chronic mild stress	25 mg/kg administered orally	Modulates the gut flora to promote 5-HTP synthesis.	38
Eucommia ulmoides	Mice subjected to chronic stress induced by electric foot shock and restraint	200 or 400 mg/kg/day administered orally for 7 days	Enhanced synapsin I expression, which in turn promoted serotonin release.	39
Fraxinus rhynchophylla	Mice subjected to chronic stress induced by electric foot shock and restraint	-	Modulation of serotonin	40
Cordia dichotoma	CUMS rats	-	Regulates the transmission of serotonergic neurons	41
Sceletium tortuosum	Chick anxiety-depression model	10, 20, 30, 50, 75, or 100 mg/kg administered intraperitoneally	Mesembrine, an established serotonin reuptake inhibitor (SRI), is present in the extract.	42
Cannabis sativa	-	-	Regulation of the activity of the serotonin receptors 1B (HTR1B) and 7 (HTR7) receptors	43
Red pomegranate fruit extract	C57BL/6 male mice	1.0, 1.5, and 2.0 mg/g	Upregulation of 5-hydroxytryptamine production	44
Ginseng fruit saponins	Sprague-Dawley rats	20 mg/kg administered orally	It acts by influencing the synthesis, release, or reuptake of serotonin in the brain	45
Acorus tatarinowii	CUMS rats	-	Enhancements in SERT function	46
persimmon leaf extract	Mice subjected to chronic social defeat stress (CSDS)	30.0–60.0 mg/kg administered orally	Limits the re-uptake of serotonin	47
Mimosa pudica	Mice	400 mg/kg administered orally for 15 days	Managing serotonin levels	48
Vaccinium bracteatum	CRS rat	-	Inhibition of 5-HT6 receptor activity	49
Punica granatum	Ovariectomized rats	1 mg/kg administered intraperitoneally	Regulation of systems involved in serotonin signaling	50
Cannabidiol	Mice	10 mg/kg administered intraperitoneally	Enhance serotonin signaling	51

by an ethanolic extract of *Tylophora indica* via adjusting brain dopamine levels. The research primarily examined anxiety, but the fact that this extract modulates dopamine, a neurotransmitter that is also involved in depression, suggests that it may have therapeutic promise in mood-related diseases. Bamboo (*Bambusa vulgaris*) and *Pogostemon cablin* (patchouli oil) have both shown dopaminergic action. A study conducted by Astuti et al.[53] found that patchouli oil had an antidepressant-like effect in rats by increasing dopamine levels and improving dopamine transmission. Also, *Bambusa vulgaris* extract may help with depression symptoms as it increased dopamine transmission in rats that had motor deficits and non-motor symptoms caused by haloperidol.[54]

Investigations into S4, terpineol, and *Garcinia cambogia* have provided further evidence that plant extracts play a part in dopamine regulation. Through the use of a chronic unpredictable mild stress (CUMS) model of depression, Yan et al.[32] showed that S4 elevated dopamine levels in the prefrontal cortex and dorsal raphe nucleus of rats. S4 had the same effect as traditional dopamine reuptake inhibitors by increasing the availability of dopamine at synapses. Through its interactions with the cannabinoid system and D2 dopamine receptors, the monoterpene terpineol demonstrated antidepressant-like effects, according to Vieira et al..[55] Terpineol promoted movement in the forced swimming test and sucrose preference test, suggesting antidepressant benefits via activating cannabinoid receptors and improving dopamine receptor function. Furthermore, a study conducted by Ibrahim et al.[35] found that *Garcinia cambogia* extract influenced dopaminergic activity in male Swiss albino mice. This effect was seen to change anxiety levels, sociability, and dopamine turnover. These natural chemicals show promise as potential plant-based antidepressants because they increase dopamine availability or activity.

1.2.3. Modulation of Norepinephrine levels in depression

Multiple investigations into the antidepressant effects of natural substances and plant extracts have focused on their ability to modulate norepinephrine, a crucial neurotransmitter in mood regulation (Table 3). The neurotransmitter norepinephrine is involved in the brain's arousal and stress response systems, and problems with its regulation are often associated with mood disorders. A study conducted by Khan et al.[56] investigated the possible psychological effects of brown seaweed in rats and found that it might raise brain norepinephrine levels. The results of this study are in line with the growing body of research that suggests reestablishing norepinephrine homeostasis might be an effective strategy for treating depression.

Following a similar line of thought, Talebi et al.[57] showed that aqueous extracts of *Melissa officinalis* and *Nepeta menthoides* synergistically reduced reserpine-induced mood disorders in mice. Reserpine causes a depressed phenotype in animal models by depleting norepinephrine reserves. Depression symptoms were dramatically reduced by taking these two plant extracts at the same time, and this improvement was associated with elevated brain norepinephrine levels. The release of norepinephrine into the synaptic cleft was thought to be caused by a two-pronged process: first, an increase in norepinephrine production; and second, a decrease in its re-uptake. Combinations of plant-based therapies, rather than treatments based on a single extract, may be able to provide higher antidepressant effects due to this complex process.

Table 2: Plants modulating dopamine levels to treat depression

Extract	*Animal model*	*Dose*	*Mechanism*	*Reference*
Cannabis sativa, *Nicotiana tabacum*, and *Carica papaya*	Male Wistar rats	5, 50, 500, and 2000 mg/kg administered orally for 90 days	The extracts enhanced dopamine availability by blocking MAO.	31
Platycladus orientalis seed	CUMS model of depression	-	Blocking the reuptake of dopamine	32
Garcinia cambogia	Male Swiss albino mice	100 mg/kg, 500 mg/kg orally for 14 days	Affecting brain dopamine turnover	35
Tylophora indica	Wistar albino rats	100 mg/kg body weight administered orally	Modified brain dopamine levels	52
Pogostemon cablin	Rats	-	Controlling the release of dopamine	53
Bambusa vulgaris	Rats	100, 200, and 400 mg/kg orally	Increased transmission of dopamine	54
terpineol	Mice with lipopolysaccharide (LPS)-induced depressive-like behavior	100 mg/kg, 200 mg/kg orally	Regulation of the D2 dopamine receptor and the cannabinoid system	55

Researchers have learned more about norepinephrine regulation by studying the locus coeruleus (LC), a brain area that is essential for the production of norepinephrine. In their study on chronic stress-induced depression, Wang et al.[58] looked at how α2A adrenoceptors control the release of norepinephrine from the LC. Under stressful situations, the release of norepinephrine may be inhibited by activating inhibitory G-protein-coupled receptors known as α2A adrenoceptors. The research found that a potential strategy to treat depression might be by restoring brain norepinephrine balance via altering the activation of these receptors. Using this knowledge as a foundation, Du et al.[59] used shRNA technology to inhibit the LC's norepinephrine transporter (NET). Research has shown that decreasing NET expression might enhance norepinephrine availability in the synaptic cleft, which in turn reduces depression-like behaviors in rats.

1.2.4. Modulation of Glutamate levels in depression

The pathophysiology of depression is heavily influenced by the regulation of glutamate, the principal excitatory neurotransmitter in the brain. This is particularly true in stress-related diseases, where abnormalities in glutamate activity are associated with neuronal injury, neurotoxicity, and oxidative stress. The development and worsening of depression symptoms are both influenced by these processes. New evidence suggests that plant extracts may be useful as a treatment for depression by rebalancing the brain's glutamate circuits (Table 4). Spinach extract, for example, has been shown to modulate glutamatergic transmission and mood regulation by decreasing corticosterone levels and increasing glutamate and glutamine concentrations in the brain.[60] Daylily flower phenolic components[61] and *Ferula gummosa* root extract[62] both showed neuroprotective effects, mitigating glutamate-induced neuronal damage, according to the same investigations. Because the latter reduced corticosterone-induced toxicity as well, it may play a role in depression caused by stress.

Supporting this, research has shown that *Psilocybe cubensis* extract can modulate depressive behaviors by influencing the glutamate pathway.[63] Similarly, *Morus nigra* leaf extract has been shown to alleviate glutamate excitotoxicity and oxidative stress in the hippocampus,[64] with syringic acid being identified as a key bioactive component. The antioxidant and anti-excitotoxic potential of *Dendropanax morbifera* leaves was highlighted by their strong neuroprotective effects, which protected hippocampus cells from glutamate-induced oxidative death.[65] Inhibition of enzymes and adjustment of oxidative stress are two of the many ways in which plant extracts like *Calotropis procera* hydroethanolic leaf extract and *Turnera diffusa* (Damiana) control glutamate levels.[66,67] They show potential in treating glutamate dysregulation, which is frequent in depression, due to their multiple activities.

Not only do certain extracts have neuroprotective properties, but they can also prevent depressive-like behaviors generated by glutamate. In a study conducted by Swaminathan et al.,[68] it was found that *Tribulus terrestris* extract lowered depressive symptoms in animal models of monosodium glutamate (MSG)-induced neurotoxicity. On the other hand, Adedoyin et al.[69] found that the aqueous extract of *Ocimum gratissimum* ameliorated biochemical changes caused by MSG, with its antioxidant and neuroprotective properties playing crucial roles. Molecular studies have shown that plant-based therapies may inhibit glutamate transporters and signal transduction pathways. For example, Zhang et al.[70] found that Yueju volatile oil increased glutamate clearance via the ERK/AKT signaling pathway, which in turn reduced excitotoxicity and supported neuronal health.

The preventive properties of natural extracts also include avoiding excitotoxicity and keeping glutamate levels stable. Dos Santos et al.[71] found that the hydroalcoholic extract of *Passiflora actinia*, which contains the active ingredient isovitexin, helped to prevent glutamate-induced neurotoxicity in slices of hippocampus, which in turn supported the survival of neurons. Similarly, Li

Table 3: Plants modulating Norepinephrine levels to treat depression

Extract	*Animal model*	*Dose*	*Mechanism*	*Reference*
Brown seaweeds	Rats	60 mg/kg orally	Maximizing the effects of norepinephrine	56
Nepeta menthoides and *Melissa officinalis*	Mice	Nepeta menthoides: 50, 100, 200, 400 mg/kg; Melissa officinalis: 150, 350, 550, 750 mg/kg; combination: Nepeta menthoides 50 mg/kg with Melissa officinalis 150 mg/kg	Promote norepinephrine production while blocking its reuptake	57
Yohimbine and BRL-44408 maleate	CUMS rats	2 mg/kg via intraperitoneal injection	It enhances the release of NE via regulating the α2a adrenoceptors.	58

et al.[72] found that *Echium amoenum* ethanol extract may reduce glutamate-induced damage in retinal ganglion cells, which is a process that is important for neurodegenerative illnesses and mood disorders. Considered as a whole, these results provide strong evidence that glutamate-modulating, antioxidant, and anti-excitotoxic plant extracts might be useful in the treatment of depression, especially in situations where chronic stress or glutamate dysregulation is the root cause. These all-natural treatments have the potential to provide a comprehensive strategy for treating depression by focusing on important pathways like excitotoxicity, oxidative stress, and glutamate transporter function.

1.2.5. *Modulation of GABA levels in depression*

Research suggests that some plant extracts may have therapeutic benefits for depression and associated diseases by modulating the GABAergic system (Table 5). Şahin and Haas[74] discovered that the plants *Piper nigrum, Citrus aurantium, Ginkgo biloba,* and *Sambucus nigra* inhibit GABA transaminase (GABA-T). This suggests that these plants may improve GABAergic signaling and, thus, help with the treatment of diseases like anxiety and depression. Furthermore, GABAergic system modulation may be possible with GABA tea, as it has been shown to enhance antioxidant defenses and mood in post-stroke depression.[75]

The actions of *Artemisia indica* Linn., which affect GABA-A receptors and provide anticonvulsant, anxiolytic, and antidepressant advantages, are also connected to the GABAergic system.[76] Hernández-López and Rodríguez-Landa[77] and Cueto-Escobedo et al.[78] found that chrysin (5,7-dihydroxyflavone) enhanced GABAergic neurotransmission in ovariectomized rats, suggesting that it may have antidepressant-like effects via regulation of GABA-A receptors. Similarly, Wu et al.[79] found that vegetable soybeans with elevated GABA content, which were created by high-pressure processing, had substantial antidepressant-like effects in rats. This result was likely due to higher GABAergic neurotransmission.

Table 4: Plants modulating Glutamate levels to treat depression

Extract	*Animal model*	*Dose*	*Mechanism*	*Reference*
Spinacia oleracea	Mice	Frozen powder (FP) and ethanol extract (EE) diets administered orally	Raised glutamate and glutamine concentrations in the brain	60
Hemerocallis citrina	Rat adrenal pheochromocytoma (PC12) cell line	0.63 to 5 mg raw material/mL	Mitigates the negative effects of corticosterone and glutamate on neurons	61
Ferula gummosa	Rat adrenal pheochromocytoma (PC12) and mouse neuroblastoma (N2a) cell lines	-	Reduces the effect of glutamate on cell death	62
Psilocybe cubensis	Mice	-	Participates in glutamate pathway interactions	63
Morus nigra	Male Swiss mice	10 mg/kg	Decreases glutamate excitotoxicity in the hippocampus	64
Dendropanax morbifera	HT22 mouse hippocampal neuronal cells	-	Reduces damage caused by glutamate	65
Turnera diffusa	SH-SY5Y human neuroblastoma cells	-	Prevents damage caused by glutamate	66
Calotropis procera	Rats	30, 100, and 300 mg/kg	Intervenes in glutamatergic pathways	67
Tribulus terrestris	Rats	-	Minimizes glutamate-induced neurotoxicity by MSG	68
Ocimum gratissimum	MSG-treated rats	-	Reduces exposure to neurotoxic effects of MSG	69
Yueju volatile oil	Mice	-	Facilitates glutamate clearance	70
Passiflora actinia	Mice hippocampal slices	-	Modulates glutamate activity	71
Echium amoenum	Retinal ganglion cells (RGCs) in a glutamate and optic nerve crush injury model in rats	-	Protects neurons from glutamate-induced injury	72
3-O-Acetyl-11-keto-β-boswellic acid (AKBA)	CUMS	-	Limits the activation of glutamate receptors	73

Badaoui et al.[80] found that an aqueous latex extract from *Euphorbia resinifera* improved performance on behavioral tests including the forced swim and tail suspension, suggesting that it may have antidepressant-like effects by modulating the GABAergic system. According to Hossen et al.,[81] bioactive compounds found in *Blumea lacera* improved GABA-A receptor binding affinity and decreased immobility in the forced swim test, suggesting that it might be a natural antidepressant. By influencing the GABAergic system, *Piper cernuum* exhibited sedative, hypnotic, and antidepressant-like effects; however, its antidepressant effects were counteracted when GABA-A receptor antagonists were administered previously.[82]

The capacity of *Moringa oleifera* leaf extract to modify GABA-A receptors has been associated with its substantial antidepressant-like and anxiolytic effects, as shown by Fidelis et al.[83] Furthermore, *Abutilon indicum* improved serotonergic and GABAergic neurotransmission, which led to anxiolytic and antidepressant-like effects in mice.[84] An improved antidepressant impact in animal models was shown to coincide with the higher GABA concentration in *Sojae Semen Praeparatum*, a processed soybean product.[85]

According to Kun and Zuhua, the triterpene molecule amyrin has the ability to modulate both the activity of MAO and the levels of GABA in the hippocampus. This suggests that it may have antidepressant and anxiolytic effects.[86] The substantial antidepressant-like effects of

Table 5: Plants modulating GABA levels to treat depression

Extract	*Animal model*	*Dose*	*Mechanism*	*Reference*
Piper nigrum, *Citrus aurantium*, *Ginkgo biloba*, and *Sambucus nigra*	-	4 to 180 **µg**/mL.	Severely reduce GABA transaminase activity,	74
Camellia sinensis	Mice subjected to bilateral common carotid artery occlusion (BCCAO) to induce ischemic stroke	10 mg/kg and 20 mg/kg	Alterations to GABAergic networks	75
Artemisia indica	Mice	Carnosol: 1, 10, 30, and 100 mg/kg administered intraperitoneally Oleanolic Acid: 1, 10, 30, and 100 mg/kg administered intraperitoneally Ursolic Acid: 1, 10, 30, and 100 mg/kg administered intraperitoneally	Act upon the GABAergic network	76
Chrysin	Ovariectomized female Wistar rats	1 mg/kg administered intraperitoneally	Improving GABAergic Neurotransmission	77
Chrysin	Ovariectomized female Wistar rats	1 mg/kg administered intraperitoneally	The GABAergic system's positive regulation	78
Glycine max	CUMS rats	soybeans containing 436.05 mg/100 g of GABA	Improving GABAergic Neurotransmission	79
Euphorbia resinifera	Mice	25-75 mg/kg	Alterations to the GABAergic network	80
Blumea lacera	Swiss albino mice	100, 200, and 400 mg/kg/day	Raised affinity for binding to GABA receptors	81
Piper cernuum	Mice	200 and 400 mg/kg	Alterations to the GABAergic network	82
Moringa oleifera	Mice	100 and 200 mg/kg	Alterations to the GABAergic network	83
Abutilon indicum	Mice	100 mg/kg	Improving Neurotransmission via GABAergic and Serotonergic Mechanisms	84
Sojae Semen Praeparatum	-	-	Alterations to the GABAergic network	85
Amyrin	Mice	-	Affects hippocampal GABA levels	86
Adzuki bean sprout	Mice	-	Enhanced GABA content	87
Artemisia monosperma	Male rats	-	The GABAergic cascade modulation	88

GABA-enriched adzuki bean sprout fermented milk provide further evidence for GABA's function in mood regulation.[87] According to Elewa et al., the ethanolic extract of *Artemisia monosperma* Delile showed antidepressant-like action via acting on the central nervous system. This effect was mediated by GABAergic modulation. These findings highlight the promise of GABAergic modulators derived from plants as an alternative to conventional treatments for depression and similar mood disorders.[88]

1.2.6. Plants affecting multiple neurotransmitters

The antidepressant effects of several plant extracts have been shown to modulate the levels of serotonin, dopamine, and norepinephrine. In comparison to traditional SSRIs, the Sceletium extract (TrimesemineTM), improves these neurotransmitters and has wider benefits on neurotransmission.[89] *Bacopa monnieri* increases levels of norepinephrine, serotonin, and dopamine by inhibiting MAO-A.[90] In a model of depression generated by reserpine, cinnamon bark (*Cinnamomum zeylanicum*) regulates these neurotransmitters to alleviate symptoms similar to depression.[91] Pigeon pea (*Cajanus cajan*) and *Ficus capensis* modulate the GABAergic system in addition to dopamine, norepinephrine, and serotonin.[92,93] In a model of chronic moderate stress, *Polygonum minus* was shown to raise levels of serotonin and norepinephrine.[94] Antidepressant and anxiolytic effects have been shown via the modulation of serotonin, dopamine, and GABA systems by the eggplant (Erythrina variegata) and the nut.[95,96] Research conducted by Adamu et al.[97] suggests that the root extract of *Moringa oleifera* may have therapeutic potential for treating symptoms of depression by increasing levels of dopamine and norepinephrine. While *Cydonia oblonga* (quince) has antidepressant-like effects via serotonin and norepinephrine modulation,[98] *Mentha piperita* (peppermint) also exhibits antidepressant-like effects by regulating serotonin, dopamine, and norepinephrine.[99] Yousuf et al.[100] found that *Acorus calamus* (sweet flag) inhibits MAO-A and MAO-B, which affects serotonin and norepinephrine levels, while Novovinty et al.[101] found that *Areca catechu* (betel nut) lowers depressive-like behaviors by modifying serotonin and norepinephrine. According to Wang et al.,[102] one of the ginsenosides found in Panax ginseng, Rb1, has antidepressant effects via modulating the systems of serotonin, norepinephrine, and dopamine.

Extraction from some plants, including *Cnestis ferruginea*, has the ability to impact the activity of serotonin, dopamine, and norepinephrine via many channels, notably cholinergic, monoaminergic, and L-arginine-nitric oxide pathways, suggesting that they may have broad-spectrum antidepressant effects.[103] Researchers have shown that the water lily *Nymphaea candida* and the daylily *Hemerocallis citrina* may treat behaviors similar to depression by modulating serotonin and other neurotransmitters.[104,105] A study conducted by Limantara et al.[106] found that *Eutherine palmifolia* may decrease behaviors associated with depression by modulating serotonin and norepinephrine. According to Youssef et al.,[107] the date palm (*Phoenix dactylifera*) and the *Salvadora persica* (miswak) plant were shown to decrease depressive-like behaviors by lowering oxidative stress and altering the serotonergic and dopaminergic systems. The levels of serotonin, dopamine, and norepinephrine can be modulated by *Synedrella nodiflora*, leading to antidepressant-like effects.[108] According to Ali and Engidawork,[109] extracts from the root bark of the *Carissa spinarum* plant control pathways that are associated with serotonin, dopamine, and noradrenaline, whereas Murtala and Akindele[110] found that *Newbouldia laevis* alleviates anxiety and depressive behaviors by regulating systems that are associated with serotonin and dopamine.

Mood modulation is facilitated by a number of plant extracts that work on the GABAergic system. According to Patro et al.,[48] *Mimosa pudica* has the ability to improve mood and decrease anxiety via increasing GABA activity and interacting with serotonin and other neurotransmitter systems. Yin et al.[111] found that beta-sitosterol and its derivatives improve mood via modulating excitatory and inhibitory neurotransmission by influencing serotonin, dopamine, and GABA. Anxiolytic and antidepressant properties of *Morinda citrifolia* are due, in part, to its actions on the $GABA_A$ receptor system, which also influence the serotonergic and adrenergic pathways.[112] According to Muhammad et al.,[113] the *Adansonia digitata* (baobab) tree has the ability to alleviate depression via influencing the GABA and glutamate neurotransmitter systems. To further enhance its antidepressant effects, erythrina variegata affects GABA activity in addition to the serotonin and dopamine systems.[95] In addition, studies have shown that passionflower (*Passiflora incarnata*) and tarragon (*Artemisia dracunculus*) both modulate GABA and serotonin systems, which in turn improve cognitive functions and reduce stress.[114,115]

Cherry leaf decoction is one plant extract that has been shown to alleviate depression symptoms by regulating the glutamate (Glu)/GABA- glutamine (Gln) metabolic loop.[116] The antioxidant, serotonergic, dopaminergic, and GABAergic systems are all stimulated by the bark extract of *Terminalia arjuna*, which in turn improves mood.[117] By influencing the systems that regulate dopamine and serotonin, *Carthamus tinctorius*, more commonly known as safflower, may have effects similar to those of antidepressants.[118] Okra (*Abelmoschus esculentus*) and oats (Avena sativa) are able to modulate the glutamate, norepinephrine, dopamine, and serotonin pathways, which

in turn produce effects similar to antidepressants.[119,120] Furthermore, new combinations of plant extracts, such as Antistress I and II[121] and crocetin,[122] have been shown to have effects similar to antidepressants and boost cognition via monoamine regulation.

1.3. Future prospects

Despite the promising results, there are still many obstacles to overcome before plant extracts can fully modulate the neurotransmitter systems implicated in depression. To further understand how these extracts impact GABA and glutamate neurotransmitter pathways, more studies into their molecular processes are needed. To further evaluate their effectiveness, safety, and ideal human doses, additional extensive clinical studies are required. Modern drug delivery technologies could improve the bioavailability of these extracts, potentially enhancing their therapeutic promise. Personalized therapy, which considers individual variations in genetics and biochemistry, could maximize treatment results. Lastly, the potential synergistic effects of mixing plant extracts with standard antidepressants call for more investigation into combination therapy.

The discovery and standardization of plant extracts' active phytochemicals are another exciting prospect for further research. This has the potential to reduce treatment variability in plant-based medicines and bring about more consistent therapeutic results. The development of high-throughput screening technologies for molecules with antidepressant-like properties might accelerate the identification of novel plant-derived candidates. Investigating plant extracts' potential to reduce depression recurrence or enhance the long-term effectiveness of existing antidepressants could provide a deeper understanding of their wider role in mental illness treatment.

2. CONCLUSION

Plant extracts may have therapeutic promise in the treatment of depression due to the involvement of neurotransmitter dysregulation in the disorder. As a potential substitute or supplement to conventional antidepressants, natural extracts have the ability to regulate levels of neurotransmitters such as serotonin, dopamine, norepinephrine, glutamate, and GABA. Although the present study indicates that these extracts have promise, further research is necessary to completely understand their mechanisms, safety, and effectiveness. More investigation into the potential of plant-based remedies for depression might lead to the creation of more tailored and efficient treatments for individuals suffering from the disorder. Furthermore, the combination of traditional knowledge with contemporary scientific discoveries may expedite the discovery of novel plant-based antidepressant drugs. This strategy has the potential to alleviate depression by offering therapy alternatives that are accessible, natural, and have low side effects.

REFERENCES

1. Santomauro DF, Herrera AM, Shadid J, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. The Lancet. 2021;398(10312):1700-1712.
2. Uher R, Payne JL, Pavlova B, Perlis RH. Major depressive disorder in DSM-5: Implications for clinical practice and research of changes from DSM-IV. Depression and anxiety. 2014;31(6):459-471.
3. Boyce P, Hopwood M, Morris G, et al. Switching antidepressants in the treatment of major depression: when, how and what to switch to?. Journal of affective disorders. 2020;261:160-163.
4. Ho TC, Gutman B, Pozzi E, Grabe HJ, et al. Subcortical shape alterations in major depressive disorder: Findings from the ENIGMA major depressive disorder working group. Human brain mapping. 2022;43(1):341-351.
5. Fries GR, Saldana VA, Finnstein J, Rein T. Molecular pathways of major depressive disorder converge on the synapse. Molecular Psychiatry. 2023;28(1):284-297.
6. Liu SH, Du Y, Chen L, Cheng Y. Glial cell abnormalities in major psychiatric diseases: A systematic review of postmortem brain studies. Molecular neurobiology. 2022;59(3):1665-1692.
7. Shyn SI, Hamilton SP. The genetics of major depression: moving beyond the monoamine hypothesis. Psychiatric Clinics. 2010;33(1):125-140.
8. Briones-Aranda A, Corzo-Gómez J, Casique-Aguirre D, Megchún-Hernández M. The platelet serotonergic system and the search for new biomarkers and therapeutic options for diverse diseases. InSerotonin-Neurotransmitter and Hormone of Brain, Bowels and Blood 2023. IntechOpen. https://www.intechopen.com/chapters/1164560. Accessed on 17 Jan 2025.
9. Tagliarini C, Carbone MG, Pagni G, Marazziti D, Pomara N. Is there a relationship between morphological and functional platelet changes and depressive disorder?. CNS spectrums. 2022;27(2):157-190.
10. Sessa F, Polito R, Li Rosi G, et al. Neurobiology and medicolegal aspects of suicides among older adults: a narrative review. Frontiers in Psychiatry. 2024;15:1449526.
11. Lin J, Liu W, Guan J, Cui J, Shi R, Wang L, Chen D, Liu Y. Latest updates on the serotonergic system in depression and anxiety. Frontiers in Synaptic Neuroscience. 2023;15:1124112.
12. De Deurwaerdere P, Di Giovanni G. 5-HT interaction with other neurotransmitters: an overview. Progress in Brain Research. 2021;259:1-5.
13. Li Z, Ruan M, Chen J, Fang Y. Major depressive disorder: advances in neu roscience research and translational applications. Neurosci Bull. 2021a;37:863-880.
14. Kim J, Kim TE, Lee SH, Koo JW. The role of glutamate underlying treatment-resistant depression. Clinical Psychopharma-

cology and Neuroscience. 2023;21(3):429-446.

15. Guo C, Ma YY. Calcium permeable-AMPA receptors and excitotoxicity in neurological disorders. Frontiers in neural circuits. 2021;15:711564.
16. Wang S, Bian L, Yin Y, Guo J. Targeting NMDA receptors in emotional disorders: their role in neuroprotection. Brain Sci. 2022;12:1329.
17. Truong V, Cheng PZ, Lee HC, Lane TJ, Hsu TY, Duncan NW. Occipital gamma-aminobutyric acid and glutamate-glutamine alterations in major depressive disorder: An mrs study and meta-analysis. Psychiatry Research: Neuroimaging. 2021;308:111238.
18. Sarawagi A, Soni ND, Patel AB. Glutamate and GABA homeostasis and neurometabolism in major depressive disorder. Frontiers in psychiatry. 2021;12:637863.
19. Cutler AJ, Mattingly GW, Maletic V. Understanding the mechanism of action and clinical effects of neuroactive steroids and GABAergic compounds in major depressive disorder. Translational Psychiatry. 2023;13(1):228.
20. Kantrowitz JT, Dong Z, Milak MS, et al. Ventromedial prefrontal cortex/anterior cingulate cortex Glx, glutamate, and GABA levels in medication-free major depressive disorder. Translational psychiatry. 2021;11(1):419.
21. Della Vecchia A, Arone A, Piccinni A, Mucci F, Marazziti D. GABA system in depression: impact on pathophysiology and psychopharmacology. Current Medicinal Chemistry. 2022;29(36):5710-5730.
22. Bhatti NA, Jobilal A, Asif K, et al. Exploring novel therapeutic approaches for depressive disorders: the role of allopregnanolone agonists. Cureus. 2023;15(8).
23. Anderson KM, Collins MA, Kong R, Fang K, Li J, He T, et al. Convergent molecular, cellular, and cortical neuroimaging signatures of major depressive disorder. Proc Natl Acad Sci USA. 2020;117:25138-25149
24. Li J, Seidlitz J, Suckling J, Fan F, Ji GJ, Meng Y, et al. Cortical structural differences in major depressive disorder correlate with cell type-specific transcriptional signatures. Nat Commun. 2021b;12:1647.
25. Gunduz-Bruce H, Takahashi K, Huang MY. Development of neuroactive steroids for the treatment of postpartum depression. J Neuroendocrinol. 2022;34:e13019.
26. Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of central and per ipheral gamma-aminobutyric acid levels in patients with unipolar and bipolar depression. J Psychiatry Neurosci. 2018;43:58-66.
27. Thakur S, Pendyala V. molecular docking studies of bioactive compounds from the alcoholic and chloroform fractions of *Callistemon citrinus* against serotonin transporter protein. World Journal of Pharmaceuticle Research. 2017;7(2):993-1004.
28. Luo LY, Xue R, Wang TG, et al. The ethanolic extract of Osmanthus fragrans var. thunbergii flowers ameliorates depressive-like behaviors of mice by modulating the serotonin system and suppressing neuroinflammation. Food Science & Nutrition. Food Sci Nutr. 2024;12(9):6242-6258
29. Sharma A, Singh T, Pathak D, Virmani T, Kumar G, Alhalmi A. Antidepressive-Like Effect of Aegle marmelos Leaf Extract in Chronic Unpredictable Mild Stress-Induced Depression-Like Behaviour in Rats. BioMed research international. 2022;2022(1):6479953.
30. Sabti M, Sasaki K, Gadhi C, Isoda H. Elucidation of the molecular mechanism underlying Lippia citriodora (Lim.)-induced relaxation and anti-depression. International journal of molecular sciences. 2019;20(14):3556.
31. Fasakin OW, Oboh G, Ademosun AO, Lawal AO. The modulatory effects of alkaloid extracts of Cannabis sativa, Datura stramonium, Nicotiana tabacum and male Carica papaya on neurotransmitter, neurotrophic and neuroinflammatory systems linked to anxiety and depression. Inflammopharmacology. 2022;30(6):2447-2476.
32. Yan L, Wang J, He X, Jin Y, et al. Platycladus orientalis seed extract as a potential triple reuptake MAO inhibitor rescue depression phenotype through restoring monoamine neurotransmitters. Journal of Ethnopharmacology. 2022;295:115302.
33. Oh DR, Yoo JS, Kim Y, et al. Vaccinium bracteatum leaf extract reverses chronic restraint stress-induced depression-like behavior in mice: regulation of hypothalamic-pituitary-adrenal axis, serotonin turnover systems, and ERK/Akt phosphorylation. Frontiers in pharmacology. 2018;9:604.
34. Li R, Wang ZM, Wang Y, Dong X, et al. Antidepressant activities and regulative effects on serotonin transporter of Nardostachys jatamansi DC. Journal of Ethnopharmacology. 2021c;268:113601.
35. Ibrahim MK, Aboelsaad M, Tony F, Sayed M. Garcinia camobogia extract alters anxiety, sociability, and dopamine turnover in male Swiss albino mice. SN Applied Sciences. 2022;4:1-7.
36. Lax NC, Parker SA, Hilton EJ, Seliman Y, Tidgewell KJ, Kolber BJ. Cyanobacterial extract with serotonin receptor subtype 7 (5-HT7R) affinity modulates depression and anxiety-like behavior in mice. Synapse. 2018;72(11):e22059.
37. Kukuia KK, Appiah F, Dugbartey GJ, et al. Extract of Mallotus oppositifolius (Geiseler) Müll. Arg. increased prefrontal cortex dendritic spine density and serotonin and attenuated para-chlorophenylalanine-aggravated aggressive and depressive behaviors in mice. Frontiers in Pharmacology. 2022;13:962549.
38. Zhang ZW, Gao CS, Zhang H, et al. Morinda officinalis oligosaccharides increase serotonin in the brain and ameliorate depression via promoting 5-hydroxytryptophan production in the gut microbiota. Acta Pharmaceutica Sinica B. 2022;12(8):3298-3312.
39. Wu J, Chen H, Li H, Tang Y, et al. Antidepressant potential of chlorogenic acid-enriched extract from Eucommia ulmoides Oliver bark with neuron protection and promotion of serotonin release through enhancing synapsin I expression. Molecules. 2016;21(3):260.
40. Kim YR, Park BK, Kim YH, et al. Antidepressant effect of Fraxinus rhynchophylla Hance extract in a mouse model of chronic stress-induced depression. BioMed research international. 2018;2018(1):8249563.
41. Wusiman Z, Tuerxunmaimaiti H, Nijiati Y, et al. Cordia dichotoma fruits aqueous extracts alleviates depressive-like behavior in a rat model via regulating serotonergic neurotransmitters. Revista Brasileira de Farmacognosia. 2024;34(2):261-269.
42. Carpenter JM, Jourdan MK, Fountain EM, et al. The effects of Sceletium tortuosum (L.) NE Br. extract fraction in the chick anxiety-depression model. Journal of ethnopharmacology. 2016;193:329-232.

43. Dosumu OA, Taiwo OA, Akinloye OA, Obadina AO, Rotimi SO, Owolabi OP, Ojo OA. Implications of Cannabis sativa on serotonin receptors 1B (HTR1B) and 7 (HTR7) genes in modulation of aggression and depression. Vegetos. 2022;35:19-25.
44. Zhu X, Sun-Waterhouse D, Cui C. A red pomegranate fruit extract-based formula ameliorates anxiety/depression-like behaviors via enhancing serotonin (5-HT) synthesis in C57BL/6 male mice. Food Science and Human Wellness. 2021;10(3):289-296.
45. Liu MY, Ren YP, Zhang LJ, Ding JY. Pretreatment with ginseng fruit saponins affects serotonin expression in an experimental comorbidity model of myocardial infarction and depression. Aging and disease. 2016;7(6):680.
46. Zhang FH, Wang ZM, Liu YT, et al. Bioactivities of serotonin transporter mediate antidepressant effects of Acorus tatarinowii Schott. Journal of ethnopharmacology. 2019;241:111967.
47. Yu H, Shao S, Xu J, Guo H, Zhong Z, Xu J. Persimmon leaf extract alleviates chronic social defeat stress-induced depressive-like behaviors by preventing dendritic spine loss via inhibition of serotonin reuptake in mice. Chinese Medicine. 2022;17(1):65.
48. Patro G, Bhattamisra SK, Mohanty BK. Effects of Mimosa pudica L. leaves extract on anxiety, depression and memory. Avicenna journal of phytomedicine. 2016;6(6):696.
49. Oh DR, Choi C, Kim MJ, et al. Antidepressant effects of p-coumaric acid isolated from Vaccinium bracteatum leaves extract on chronic restraint stress mouse model and antagonism of serotonin 6 receptor in vitro. Phytomedicine. 2023;116:154871.
50. Valdés-Sustaita B, Estrada-Camarena E, González-Trujano ME, López-Rubalcava C. Estrogen receptors-β and serotonin mediate the antidepressant-like effect of an aqueous extract of pomegranate in ovariectomized rats. Neurochemistry International. 2021;142:104904.
51. Sales AJ, Crestani CC, Guimarães FS, Joca SR. Antidepressant-like effect induced by Cannabidiol is dependent on brain serotonin levels. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;86:255-261.
52. Manikkoth S, Deepa B, Sequeira M, Joy AE, Rodrigue R. Assessment of brain dopamine levels to evaluate the role of tylophora indicaethanolic extract on alcohol induced anxiety in Wistar albino rats. Journal of Young Pharmacists. 2016;8(2):91.
53. Astuti P, Khairan K, Marthoenis M, Hasballah K. Antidepressant-like activity of patchouli oil var. Tapak Tuan (Pogostemon cablin Benth) via elevated dopamine level: a study using rat model. Pharmaceuticals. 2022;15(5):608.
54. Murtala AA, Oladapo OE, Oladoja FA, et al. Bambusa vulgaris attenuates Haloperidol-induced motor deficit and non-Motor co-morbidity in rats through up-regulation of Dopamine transmission and mitigation of pro-inflammatory cytokines activities. Pharmacological Research-Modern Chinese Medicine. 2024;10:100375.
55. Vieira G, Cavalli J, Gonçalves EC, et al. Antidepressant-like effect of terpineol in an inflammatory model of depression: involvement of the cannabinoid system and D2 dopamine receptor. Biomolecules. 2020;10(5):792.
56. Khan A, Uddin N, Khaliq S, Nawaz S, et al. Brown seaweeds administration generate psychotherapeutic response associated with brain norepinephrine modulation in rats. Journal of Pharmacognosy and Phytotherapy. 2017;9(1):11-18.
57. Talebi S, Rahmati B, Jorjani M, et al. Synergistic effects of Nepeta menthoides and Melissa officinalis aqueous extracts on reserpine-induced depressive-like behaviors in mice. Phytotherapy Research. 2022;36(6):2481-2494.
58. Wang GL, He ZM, Zhu HY, et al. Involvement of serotonergic, noradrenergic and dopaminergic systems in the antidepressant-like effect of ginsenoside Rb1, a major active ingredient of Panax ginseng CA Meyer. Journal of Ethnopharmacology. 2017;204:118-124.
59. Du X, Yin M, Yuan L, et al. Reduction of depression-like behavior in rat model induced by ShRNA targeting norepinephrine transporter in locus coeruleus. Translational Psychiatry. 2020;10(1):130.
60. Son H, Jung S, Shin JH, Kang MJ, Kim HJ. Anti-stress and anti-depressive effects of spinach extracts on a chronic stress-induced depression mouse model through lowering blood corticosterone and increasing brain glutamate and glutamine levels. Journal of Clinical Medicine. 2018;7(11):406.
61. Tian H, Yang FF, Liu CY, et al. Effects of phenolic constituents of daylily flowers on corticosterone-and glutamate-treated PC12 cells. BMC complementary and alternative medicine. 2017;17:1-2.
62. Sadeghnia HR, Rajabian A, Ghorbani A, Moradzadeh M, Hosseini A. Effects of standardized extract of Ferula gummosa root on glutamate-induced neurotoxicity. Folia neuropathologica. 2017;55(4):340-346.
63. Mahmoudi E, Faizi M, Hajiaghaee R. Alteration of depressive-like behaviors by Psilocybe cubensis alkaloid extract in mice: the role of glutamate pathway. Research Journal of Pharmacognosy. 2018;5(2):17-24.
64. Dalmagro AP, Camargo A, Pedron NB, Garcia SA, Zeni AL. Morus nigra leaves extract revokes the depressive-like behavior, oxidative stress, and hippocampal damage induced by corticosterone: a pivotal role of the phenolic syringic acid. Behavioural Pharmacology. 2020;31(4):397-406.
65. Park HJ, Kwak M, Baek SH. Neuroprotective effects of Dendropanax morbifera leaves on glutamate-induced oxidative cell death in HT22 mouse hippocampal neuronal cells. Journal of ethnopharmacology. 2020;251:112518.
66. Bernardo J, Ferreres F, Gil-Izquierdo Á, Valentao P, Andrade PB. Medicinal species as MTDLs: Turnera diffusa Willd. Ex Schult inhibits CNS enzymes and delays glutamate excitotoxicity in SH-SY5Y cells via oxidative damage. Food and Chemical Toxicology. 2017;106:466-476.
67. Obese E, Biney RP, Henneh IT, et al. Antinociceptive effect of the hydroethanolic leaf extract of Calotropis procera (Ait) R. Br.(Apocynaceae): possible involvement of glutamatergic, cytokines, opioidergic and adenosinergic pathways. Journal of Ethnopharmacology. 2021;278:114261.
68. Swaminathan G, Jupudi S, NS R. Tribulus terrestris Linn Attenuates Neurotoxicity Induced By Monosodium-Glutamate: An In Vivo Evidence. International Journal of Pharmaceutical Research. 2021;13(1):2065-2075.
69. Adedoyin D, Ojokuku AS, Bamidele FA. The Effect of Aqueous Extract of Ocimum gratissimum On Monosodium Glutamate Induced Biochemical Changes in Albino Rats. Tropical Journal of Natural Product Research. 2020;4(2):27-30
70. Zhang B, Su D, Song Y, Li H, et al. Yueju volatile oil plays an integral role in the antidepressant effect by up-regulating ERK/AKT-mediated GLT-1 expression to clear glutamate.

Fitoterapia. 2023;169:105583.

71. Dos Santos KC, Borges TV, Olescowicz G, Ludka FK, Santos CA, Molz S. Passiflora actinia hydroalcoholic extract and its major constituent, isovitexin, are neuroprotective against glutamate-induced cell damage in mice hippocampal slices. Journal of Pharmacy and Pharmacology. 2016;68(2):282-291.
72. Li H, Behnammanesh G, Wu Z, Rong R, You M, Majid AS, Ji D. Echium amoenum L. ethanol extract protects retinal ganglion cell after glutamate and optic nerve crush injury. Disease Markers. 2022a;2022(1):3631532.
73. Gunasekaran V, Augustine A, Avarachan J, Khayum A, Ramasamy A. 3-O-Acetyl-11-keto-β-boswellic acid ameliorates chronic unpredictable mild stress induced HPA axis dysregulation in relation with glutamate/GABA aberration in depressive rats. Clinical and Experimental Pharmacology and Physiology. 2021;48(12):1633-1641.
74. Şahin S, Haas S. GABAergic effects of some foods extracts via inhibition of GABA transaminase (GABA-T). Middle Black Sea Journal of Health Science. 2021;7(3):423-428.
75. Daglia M, Di Lorenzo A, Nabavi SF, Sureda A, et al. Improvement of antioxidant defences and mood status by oral GABA tea administration in a mouse model of post-stroke depression. Nutrients. 2017;9(5):446.
76. Khan I, Karim N, Ahmad W, Abdelhalim A, Chebib M. GABA-A receptor modulation and anticonvulsant, anxiolytic, and antidepressant activities of constituents from artemisia indica Linn. Evidence-Based Complementary and Alternative Medicine. 2016;2016(1):1215393.
77. Cueto-Escobedo J, Andrade-Soto J, Lima-Maximino M, et al. Involvement of GABAergic system in the antidepressant-like effects of chrysin (5, 7-dihydroxyflavone) in ovariectomized rats in the forced swim test: comparison with neurosteroids. Behavioural Brain Research. 2020;386:112590.
78. Hernández-López F, Rodríguez-Landa JF. Involvement of GABAergic system in the antidepressant-like effects of. Behavioural Brain Research. 2020;386:112590.
79. Wu SJ, Chang CY, Lai YT, Shyu YT. Increasing γ-aminobutyric acid content in vegetable soybeans via high-pressure processing and efficacy of their antidepressant-like activity in mice. Foods. 2020;9(11):1673.
80. Badaoui M, Moubtakir S, Terrafe C, Aboufatima R, Chait A. Antianxiety and antidepressant effects of aqueous latex extract of Euphorbia resinifera. Bangladesh Journal of Pharmacology. 2022;17(2):32-41.
81. Hossen MA, Ali Reza AS, Amin MB, et al. Bioactive metabolites of Blumea lacera attenuate anxiety and depression in rodents and computer-aided model. Food Science & Nutrition. 2021;9(7):3836-3851.
82. Maia MA, Jurcevic JD, Malheiros A, et al. Neuropharmacology potential of the hydroalcoholic extract from the leaves of Piper cernuum: anxiolytic, hypnotic, and antidepressant-like effects. Evidence-Based Complementary and Alternative Medicine. 2023;2023(1):1183809.
83. Fidelis KR, Alves RR, Patriota LL, et al. Saline extract from Moringa oleifera Leaves has antidepressant and anxiolytic effects in mouse models. Nutraceuticals. 2024;4(1):65-81.
84. Zhou X, Hassan W, Bakht S, Hussain K, Ahmed H. Abutilon indicum exhibits anxiolytic and antidepressant effects in mice models. Dokl Biochem Biophys. 2021;500(1):341-346.
85. Chen QF, He J, Xie XM, Wang LY, Xie WH, Su MS, Luo XQ, Long K. Determination of content of γ-aminobutyric acid and its antidepressant effect at different time points during processing of Sojae Semen Praeparatum. Drug Evaluation Research. 2021;44(4):688-694
86. Kun X, Zuhua G. Amyrin exerts potent anxiolytic and antidepressant effects via mechanisms involving monoamine oxidase and γ-aminobutyric acid in mouse hippocampus. Tropical Journal of Pharmaceutical Research. 2019;18(8):1673-1681.
87. Wu Z, Wang P, Pan D, Zeng X, Guo Y, Zhao G. Effect of adzuki bean sprout fermented milk enriched in γ-aminobutyric acid on mild depression in a mouse model. Journal of Dairy Science. 2021;104(1):78-91.
88. Bakrim S, Benkhaira N, Bourais I, Benali T, Lee LH, El Omari N, Sheikh RA, Goh KW, Ming LC, Bouyahya A. Health benefits and pharmacological properties of stigmasterol. Antioxidants. 2022;11(10):1912.
89. Coetzee DD, López V, Smith C. High-mesembrine Sceletium extract (Trimesemine™) is a monoamine releasing agent, rather than only a selective serotonin reuptake inhibitor. Journal of ethnopharmacology. 2016;177:111-116.
90. Alkahtani J, Elshikh MS, Dwiningsih Y, Rathi MA, Sathya R, Vijayaraghavan P. In-vitro antidepressant property of methanol extract of Bacopa monnieri. Journal of King Saud University-Science. 2022;34(8):102299.
91. Ghaderi H, Rafieian M, Nezhad HR. Effect of hydroalcoholic Cinnamomum zeylanicum extract on reserpine-induced depression symptoms in mice. Pharmacophore. 2018;9(2-2018):35-44.
92. Olubodun-Obadun TG, Ishola IO, Adesokan TP, Anih BO, Adeyemi OO. Antidepressant-and anxiolytic-like actions of Cajanus cajan seed extract mediated through monoaminergic, nitric oxide-cyclic GMP and GABAergic pathways. Journal of Ethnopharmacology. 2023;306:116142.
93. Patil S, Nargatti P, Shikalgar T, Naikwade N. Evaluation of Antidepressant activity of Ficus carica leaves extract in experimental animals. Research Journal of Pharmacy and Technology. 2021;14(3):1267-73.
94. Bashir MI, Abdul Aziz NH, Noor DA. Antidepressant-like effects of polygonum minus aqueous extract in chronic ultra-mild stress-induced depressive mice model. Behavioral Sciences. 2022;12(6):196.
95. Chu HB, Tan YD, Li YJ, et al. Anxiolytic and anti-depressant effects of hydroalcoholic extract from Erythrina variegata and its possible mechanism of action. African Health Sciences. 2019;19(3):2526-2536.
96. Jawaid T, Tiwari N, Kamal M, et al. Evaluation of antidepressant and anxiolytic activity of Solanum melongena L. fruits aqueous extract via monoaminergic and GABAergic pathway. Journal of Pharmaceutical Research International. 2020;31(6):1-9.
97. Adamu A, Jada MS, Saidu U, Usha YI, Favour EG, Shuaibu MN. Moringa oleifera (Lam) root extracts elevate catecholamine levels in experimental rats: potential role of ethnopharmacology in combating depressive conditions. Jordan Journal of Biological Sciences. 2023;16(2).
98. Ganaie MU, Behl T, Nijhawan P, Sachdeva M, Khan N. Investigation of anti-depressant effect of aqueous and ethanolic extract of Cydonia oblonga in rats. Obesity Medicine.

2020;18:100202.

99. Abbasi-Maleki S, Bakhtiarian A, Nikoui V. Involvement of the monoaminergic system in the antidepressant-like effect of the crude extract of Mentha piperita (Lamiaceae) in the forced swimming test in mice. Synergy. 2017;5:21-28.
100. Yousuf S, Haq SM, Rasool A, et al. Evaluation of antidepressant activity of methanolic and hydroalcoholic extracts of Acorus calamus L. rhizome through tail suspension test and forced swimming test of mice. Journal of Traditional Chinese Medical Sciences. 2020;7(3):301-307.
101. Novianty R, Sofiyanti N, Indriani DW, Wasito H, Ya'la FA. Potential antidepressant activity of n-hexane extract from old Areca catechu Nut by reducing depressive-like state in Swiss albino male mice. Current Research on Biosciences and Biotechnology. 2024;6(1):6-12.
102. Wang B, Wang Y, Wu Q, Huang HP, Li S. Effects of α2A adrenoceptors on norepinephrine secretion from the locus coeruleus during chronic stress-induced depression. Frontiers in Neuroscience. 2017;11:243.
103. Owope TE, Ishola IO, Akinleye MO, Oyebade R, Adeyemi OO. Antidepressant effect of cnestis ferruginea Vahl ex DC (Connaraceae): involvement of cholinergic, monoaminergic and L-arginine-nitric oxide pathways. Drug Research. 2016;66(05):235-245.
104. Hong H, Gao M, Zhou M, et al. Ethyl acetate extract of Nymphaea candida Presl: A potential anti-depressant and neuroprotective treatment strategy. Biomedicine & Pharmacotherapy. 2024;179:117304.
105. Xu P, Wang KZ, Lu C, et al. Antidepressant-like effects and cognitive enhancement of the total phenols extract of Hemerocallis citrina Baroni in chronic unpredictable mild stress rats and its related mechanism. Journal of Ethnopharmacology. 2016;194:819-826.
106. Hosseini SE, Hosseini SA. The therapeutic effects of medicinal plants on depression and anxiety disorders. Report of Health Care. 2018 Mar 1;4(1):67-80.
107. Youssef B, Ramadan KS, ElShebiney S, Ibrahim EA. Antidepressant-like effects of aqueous extracts of miswak (Salvadora persica) and date palm (Phoenix dactylifera) on depression-like behaviors using CUMS model in male rats. Journal of Food Biochemistry. 2022;46(8):e14164.
108. Amoateng P, Kukuia KK, Mensah JA, et al. An extract of Synedrella nodiflora (L) Gaertn exhibits antidepressant properties through monoaminergic mechanisms. Metabolic brain disease. 2018;33:1359-1368.
109. Ali HS, Engidawork E. Antidepressant-Like Activity of Solvent Fractions of the Root Bark of Carissa spinarum Linn. (Apocynaceae) in Rodents Involves Multiple Signaling Pathways. Journal of Experimental Pharmacology. 2022:379-394.
110. Murtala AA, Akindele AJ. Anxiolytic-and antidepressant-like activities of hydroethanol leaf extract of Newbouldia laevis (P. Beauv.) Seem.(Bignoniaceae) in mice. Journal of ethnopharmacology. 2020;249:112420.
111. Yin Y, Liu X, Liu J, et al. The effect of beta-sitosterol and its derivatives on depression by the modification of 5-HT, DA and GABA-ergic systems in mice. RSC advances. 2018;8(2):671-680.
112. Narasingam M, Vijeepallam K, Mohamed Z, Pandy V. Anxiolytic-and antidepressant-like activities of a methanolic extract of Morinda citrifolia Linn.(noni) fruit in mice: Involvement of benzodiazepine-GABAAergic, serotonergic and adrenergic systems. Biomedicine & Pharmacotherapy. 2017;96:944-952.
113. Muhammad A, Hamman LL, Chiroma SM, Attah MO, Dibal NI. Adansonia digitata L. stem bark attenuates epileptic seizure, depression, and neurodegeneration by mediating GABA and glutamate in pentylenetetrazol-kindled rats. Journal of Pharmacopuncture. 2023;26(4):327.
114. Jawna-Zboińska K, Blecharz-Klin K, Joniec-Maciejak I, et al. Passiflora incarnata L. improves spatial memory, reduces stress, and affects neurotransmission in rats. Phytotherapy Research. 2016;30(5):781-789.
115. Ilkhanizadeh A, Asghari A, Hassanpour S, Safi S. Antidepressant effect of Artemisia dracunculus extract is mediated via GABAergic and serotoninergic systems in ovariectomized mice. Journal of Basic and Clinical Pathophysiology. 2021;9(2):32-41.
116. Jiang C, Wang H, Qi J, et al. Antidepressant effects of cherry leaf decoction on a chronic unpredictable mild stress rat model based on the Glu/GABA-Gln metabolic loop. Metabolic Brain Disease. 2022;37(8):2883-2901.
117. Sekhar YC, Kumar GP, Anilakumar KR. Terminalia arjuna bark extract attenuates picrotoxin-induced behavioral changes by activation of serotonergic, dopaminergic, GABAergic and antioxidant systems. Chinese journal of natural medicines. 2017;15(8):584-596.
118. Abbasi-Maleki S, Mousavi Z. Hydroethanolic extract of Carthamus tinctorius induces antidepressant-like effects: modulation by dopaminergic and serotonergic systems in tail suspension test in mice. Iranian journal of basic medical sciences. 2017;20(9):1063.
119. Arraey H, Abbasi-Maleki S, Mohammadi Motamed S. Hydroalcoholic extract of Avena sativa exerts antidepressant-like effects through the monoaminergic system. Research Journal of Pharmacognosy. 2024;11(2):11-18.
120. Yan T, Nian T, Liao Z, Xiao F, Wu B, Bi K, He B, Jia Y. Antidepressant effects of a polysaccharide from okra (Abelmoschus esculentus (L) Moench) by anti-inflammation and rebalancing the gut microbiota. International journal of biological macromolecules. 2020;144:427-40.
121. Kandilarov IK, Zlatanova HI, Georgieva-Kotetarova MT, et al. Antidepressant effect and recognition memory improvement of two novel plant extract combinations-antistress I and antistress II on rats subjected to a model of mild chronic stress. Folia medica. 2018;60(1):110-116.
122. Farkhondeh T, Samarghandian S, Samini F, Sanati AR. Protective effects of crocetin on depression-like behavior induced by immobilization in rat. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2018;17(5):361-369.

How to cite this article: Swetha V, Nandini V, Pareek V, Kumar VU, Srihari V, Devi K. The role of natural extracts in depression: modulation neurotransmitters for antidepressant effects. Int. J. Appl. Pharm. Sci. Res. 2023;9(1):1-15. doi: https://doi.org/10.21477/ijapsr.9.1.01

Source of Support: Nil.

Conflict of Support: None declared.