Botanical Breakthroughs in Depression: Insights from the Cums Animal Model

Utkarsh R. Mandage.[1]*, Indrayani S. Pagare[2], Anushka S. Deore [3] Neetu V. Patil[4],

[1]Lecturer, Department of Pharmacognosy, Ravindra Vidya Prasarak Mandal Institute of Pharmacy, Dwarka, Nashik, India.

[2]Principal, Department of QA, Ravindra Vidya Prasarak Mandal Institute of Pharmacy, Dwarka, Nashik, India.

[3] Assistant Professor, Department of Pharmacognosy, MET's Institute of Pharmacy, Adgaon, Nashik, India.

[4]HOD, Department of QA, Shri Sai Samarth College of Pharmacy and Research Center, Bhadgaon, India.

ABSTRACT

Depression is a debilitating mental health condition with significant global prevalence and a profound impact on quality of life. Conventional antidepressant therapies, though effective in many cases, are often limited by delayed onset of action, side effects, and treatment resistance. Consequently, the exploration of alternative and complementary approaches, particularly those involving medicinal plants, has gained momentum in recent years. The Chronic Unpredictable Mild Stress (CUMS) model, widely used to simulate human depression in animal studies. Numerous medicinal plants have demonstrated promising antidepressant-like effects in this model, often by modulating key neurobiological pathways, such as monoaminergic transmission, hypothalamic-pituitary- adrenal (HPA) axis activity, oxidative stress, neuroinflammation, and neurotrophic factor expression (notably Brain-Derived Neurotrophic Factor, BDNF). These botanicals often exhibit multi-targeted effects, making them attractive candidates for integrative therapeutic approaches. This review highlights the evaluation of antidepressant activity of various medicinal plants extracts by specifically applying chronic unpredictable mild stress (CUMS) for particular period of time including mechanisms of action, behavioral models used (e.g., FST, TST, SPT), and comparative efficacy of various plant extracts in the CUMS model, underlining the potential of phytomedicines as viable alternatives or adjuncts in depression management.

KEYWORDS: Depression, Chronic Unpredictable Mild Stress, Hypothalamus Pitutary Adrenal axis, Medicinal plants, Antidepressants

INTRODUCTION

Depression is a mental health condition characterized by a depressed mood and a dislike of real effort. Neglect distinguishes burdensome temperament problems and slow thinking, in addition to psychomotor hindrance symptoms including a lack of enthusiasm for routine tasks, anhedonia (the inability to experience joy), and a general lack of interest. An estimated 3.8% of the world's population is affected by depression, including 5% of adults and 5.7% of people over 60. Around 280 million people worldwide suffer from the negative consequences of depression. Sadness is different from normal emotional outbursts and fleeting local responses to everyday situations.

Depression can be highly detrimental to an individual's well-being, especially when it is persistent and ranges from mild to severe. It can cause significant suffering and negatively impact performance in work, school, and family life. In extreme cases, depression can lead to suicide, with approximately 700,000 people dying each year due to suicidal actions linked to depression. Depression is a chronic, recurring condition that severely affects an individual's quality of life and overall productivity. While many types of antidepressant medications are currently available, there is a pressing need for the development of more effective and safer treatments due to the limitations and side effects of existing options. Therefore, new approaches to treating depression are essential.

Pathophysiology of depression

The pathophysiology of depression is thought to involve the serotonergic system, according to various studies. These studies have found that many antidepressants work by inhibiting the reuptake of serotonin (5-HT), thereby reducing the behavioral changes caused by chronic unpredictable mild stress (CUMS). It is believed that prolonged activation of the HPA (hypothalamic-pituitary-adrenal) axis can lead to mitochondrial damage, which then triggers an increase in serotonin flux via monoamine oxidase (MAO), resulting in the destruction

of serotonergic neurons in areas of the brain such as the hippocampus (HIP) and prefrontal cortex (PFC). In animal models of depression, Brain-Derived Neurotrophic Factor (BDNF), which plays a crucial role in neuronal survival and neurogenesis, is often linked to the expression of proinflammatory mediators. CUMS and other stress models reduce BDNF levels in the brain, while prolonged antidepressant treatment—particularly with imipramine—can alter BDNF levels during a depressive episode. Increased expression of proinflammatory mediators has been associated with lower BDNF expression in the brain. Additionally, various therapeutic strategies have been shown to have antidepressant effects by modulating BDNF-related activities, particularly by reducing the impact of proinflammatory mediators. These findings suggest a significant connection between mitochondrial function, serotonin signaling, and proinflammatory mediators in the pathogenesis of depression.[1]

Types of depression

A. Major depression

Depression symptoms that persist for longer than two weeks include anhedonia, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, diminished concentration or thought processes, and suicidal thoughts.

B. Bipolar disorder

Bipolar disorder has been classified into two categories based on the intensity of manic episodes.

1. Bipolar I disorder

Major sadness and full manic episodes—a distinct time of consistently elevated, expansive, or irritated mood that lasts for at least one week—are the hallmarks of this condition.

2. Bipolar II disorder

This condition is typified by significant sadness and hypomanic symptoms, which are similar to mania but endure for at least four days, without affecting social or professional functioning or necessitating hospitalization or psychotic symptoms.

C. Seasonal Affective Disorder (SAD)

Seasonal affective disorder (SAD) is distinct in that it responds to bright light sessions and experiences during the short days of winter.

D. Dysthymia

Instead of mood swings, it is typified by persistent depression symptoms that last for two years. Dysthymia, a persistent mild depression, is most frequently seen in primary care settings, receives fewer diagnoses and treatments, but results in substantial social and occupational impairment.

E. Cyclothymia

It is a less severe type of bipolar disorder. It is a persistent mood disorder that lasts longer than two years and is typified by recurrent episodes of depression and hypomania. The depressive episodes in cyclothymia never fit the criteria for major depression, which is how it varies from bipolar type II disorder. Although cyclothymia patients rarely need medication therapy, mood stabilizers can be helpful when needed.[2]

Classification of antidepressant drugs[3]

Class	Examples
1. Reversible inhibitors of MAO-A (RIMAs)	Moclobemide, Clorgyline
2. Tricyclic Antidepressants (TCAs)	
▪ NA & 5-HT Reuptake Inhibitors	Imipramine, Trimipramine, Amitryptyline, Doxepin, Dothiepin, Clomipramine
▪ Predominantly NA reuptake inhibitors	Desipramine, Reboxetine
3. Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram, Dapoxetine
4. Serotonin & Noradrenaline Reuptake Inhibitors (SNRIs)	Venlafaxine, Desvenlafaxine, Duloxetine
5. Atypical Antidepressants	Trazodone, Mianserin Mirtazapine, Bupropion, Amoxapine, Tianeptine, Amineptine

Chronic unpredictable mild stress

The CUMS protocol used in this study was adapted from the method developed by Willner et al. (1992) and modified for mice by Ducottet and Belzung (2004). This model involves exposing the mice to various mild physical and psychological stressors multiple times a day over a period of 7 weeks in a chronic, unavoidable, and unpredictable manner. The stressors included damp sawdust, changing the sawdust, placing the mice in an empty cage or a cage with water at the bottom (a "bath"), soiled cage bedding with an unpleasant odor, social stress (cage swapping), tilting the cage (45°), exposure to predator sounds for 15 minutes, inverting the light/dark cycle, briefly turning on the lights during the dark phase or turning them off during the light phase, and confinement in a tube. The stressors were applied in a pseudo-random order and could occur at any time, with the sequence changing every week to maintain unpredictability. During behavioral testing, the number of stressors applied during the light period was reduced

to avoid interference with the tests. The control group of mice was left undisturbed in their home cages.[4]

Behavioural models

Splash test

The Splash Test was used to evaluate the grooming behavior of mice. A 10% sucrose solution was sprayed onto the dorsal coat of the mice while they were in their home cages, and the number of grooming actions was recorded over a 5-minute period after the application of the sucrose solution [Ducottet and Belzung, 2004]. Following the test, all mice were returned to their home cages, and the observer was unaware of the treatment conditions.[4]

RIT

The Resident/Intruder Test (RIT) was conducted according to the method described by Mineur et al. (2003). Non-stressed mice were isolated for 48 hours before the test, during which their bedding was not changed to increase territorial cues in the cage. The resident mouse was tested against a C57/BL6 intruder mouse. The intruder was placed in the resident's cage in opposite corners, and the cage was covered with a plastic lid. The test began immediately and lasted for up to 5 minutes, during which the number of attacks between the resident and intruder was recorded. The observer was unaware of the treatment conditions.[4]

Tail Suspension Test (TST)

The Tail Suspension Test is a widely used behavioral model for assessing antidepressant activity in mice (Steru et al., 1985). This model measures the total duration of immobility after tail suspension, as described by Rodrigues et al. (2002) for evaluating potential antidepressants. In brief, each mouse was suspended by the tip of its tail (approximately 1 cm) 50 cm above the floor, attached to a lever. The test was conducted in isolation, and each mouse was observed for a total of 6 minutes. The first 2 minutes served as an acclimation period, while the next 4 minutes were used to manually record the duration of immobility using a stopwatch. A mouse was considered immobile when it showed no movement, hung passively, and remained completely still. The test was carried out between 8 a.m. and 12 p.m. in a quiet room to avoid disrupting the mice's biological rhythm. The procedure was repeated for each mouse in the experimental groups, which consisted of 5 mice each. Group 1 received distilled water (0.2 mL/20 g), groups 2-4 received different doses of BU (1.25, 2.5, and 5 mg/kg), and group 5 received imipramine (10 mg/kg). All treatments were administered 30 minutes before testing. [4]

Forced Swimming test (FST)

The Forced Swim Test (FST) is a behavioral assay commonly used to evaluate antidepressant activity in rodents. In this test, rodents are placed individually in Plexiglas cylinders (40 cm in height, 18 cm in diameter) filled with water maintained at 25 °C, up to a depth of 15 cm. Each trial consists of a 2-minute pre-swimming period, followed by a 4-minute test period during which the total duration of immobility is measured. Mice are considered immobile when they make no further attempts to escape and only engage in movements necessary to keep their heads above the water's surface. The absence of hind leg movement is recorded as immobility using a stopwatch during the exposure. The water in the cylinder is changed before each trial, and the mice are gently dried with a towel before being returned to their home cages after the swimming sessions.[5]

Locomotor activity in the Open Field

The open field apparatus, which consisted of a white Plexiglass box measuring 28 cm by 28 cm by 25 cm and a floor that was evenly divided into 16 equal squares marked with a painted black grid, was used to measure motor activity. Each mouse was positioned independently in the middle of the box thirty minutes after the administration of an extract or regular medication, and for five minutes, the number of squares that all four paws crossed was tallied. Before the next animal was evaluated, the floor of the open field apparatus was washed with 70% ethanol and left for five minutes (Akanmu et al., 2011).[5]

Yohimbine Induced Lethality Test

The yohimbine-induced lethality test was used to assess the extract's antidepressant-like action and the role of the noradrenergic system. The test was conducted in accordance with Vogel & Vogel's (1997) instructions. Five groups of ten mice each were created from fifty (50) mice. Group 1 was given 10 mL/kg of distilled water; groups 2-4 were given varying dosages of BU leaf extract (1.25, 2.5, and 5.0 mg/kg; i.p.); and group 5 was given imipramine (10 mg/kg; i.p.). Thirty minutes before Yohimbine (35 mg/kg; i.p.) was administered, all treatments were completed. Twenty-four hours following the Yohimbine injection, the number of fatalities and the percentage of lethality were determined.[5]

Reserpine-induced hypothermia, ptosis and diarrhea in mice

The tests for ptosis, diarrhea, and hypothermia brought on by reserpine were consistent with those conducted by Bourin et al. (1983). Thirty minutes following treatment with either distilled water, BU, or imipiramine, the mice were given reserpine (2.5 mg/kg). Five groups of male mice (n=5) received the therapy. Group 1 received 0.2 mL/20 g of distilled water, while groups 2-4 received varying dosages of BU (1.25, 2.5, and 5 mg/kg); group 5 received imipramine (10 mg/kg). Following the administration of reserpine, the rectal temperature was measured at 0, 1, 2, 3, and 4 hours, respectively. After four hours, the degree of ptosis was assessed using the following scoring system: eyes open = 0, eyes half closed = 2, eyes three-quarters closed = 3, and eyes fully closed = 4. A rectal thermometer was used to test the subject's body temperature. The thermometer's probe was placed 1.5 cm into the rectum. Temperature variations

were calculated using the pre-drug recording as a reference point (Parimaladevi et al., 2003). The number of droppings at various time points was used to measure diarrhea.[5]

Measurement of Locomotor activity by Actophotometer

A photoactometer (INCO, Ambala, India) was used to record the horizontal locomotor activity of the test and control animals for five minutes. This was done in order to rule out how different pharmacological treatments might affect locomotor activity. Photoelectric cells that are connected in circuit with a counter power the photoactometer. A count is made when an animal's movement stops the light beam from reaching the photocell (Kumar, Kuhad, Chopra, 2011).[6]

Sucrose preference test

This study used the sucrose preference test (Willner et al., 1987) to identify anhedonia, one of the main signs of serious depression in people. Before the CUMS procedure began, mice were trained to eat 1% (w/v) sucrose solution following a week of acclimatization. Mice in the training course were only given 1% w/v sucrose solution and were denied food and drink for 48 hours. Mice were given the option to choose between two pre-weighed bottles, one containing 1% w/v sucrose solution and the other containing tap water, during a 1-hour baseline test conducted three days following the 23-hour food and water deprivation. The following formula was then used to determine the sucrose preference:

Preference for sucrose (%) = A/A+B×100

Where,

A denotes the consumption of sucrose solution in grams

B denotes the intake of water in grams.

On the 22nd day, the test was conducted once more to assess the impact of medication treatments on both stressed and unstressed mice.[6]

Open-field test

The mice's exploratory and depressed behaviors were examined using the open-field test (OFT), which was conducted as previously mentioned.[21] With black side walls and a black floor that was divided into 25 equal squares by white lines, the open field apparatus was a four-sided wooden cage measuring 40 cm by 40 cm by 30 cm. For five minutes, each animal was positioned in the center square of the device, and the following behaviors were noted: the number of walks, rearings, grooming times, and immobility times.[7]

Novelty-suppressed feeding test

As previously mentioned, the novelty-suppressed feeding test (NFT) was conducted (Stedenfeld et al., 2011). Twenty-four hours before the test, the mice were denied food. In the test, a single piece of mouse chow was positioned in the middle of the 42 × 31 × 20 cm^3 box. The time until the first feeding event was noted after all of the mice were put in the box's corner and given five minutes to freely nibble on the chow. The mice were then immediately put back in their own cage, where they had unlimited access to food and water.[8]

Medicinal plants showing antidepressant activity in CUMS model of depression

Name of Plant & Family	Extract & Part used	Dose & Route	Animal Model	Method	CUMS Duration (Days)	Reference Std. Drug, dose & Route	Phytochemicals	Reference
Abelmoschus esculentus (Malvaceae)	Aqueous extract of seeds	300, 600 mg/kg p.o.	Mice	FST, TST, OFT	21	Paroxetine 10mg//kg p.o.	Polyphenols, Flavonoids	[9]
Adansonia digitata (Malvaceae)	Methanolic extract of Stem bark	250, 500 & 1000 mg/kg p.o.	Mice	TST, OFT, SPT	14	Imipramine 15 mg/kg p.o.	-	[10]
Aegle marmelos (Rutaceae)	Hydroethanolic extract of Leaves	150, 300 mg/kg p.o.	Rat	OFT, FST, TST, Sucrose Preference Test	35	Imipramine 150 mg/kg p.o.	Tannins, Alkaloids, Saponins, Glycosides, Flavonoids, Steroids, Terpenoids, Phlobatannins, Anthraquiones	[11]
Anacyclus pyrethrum (Asteraceae)	Ether extract of Roots	150, 300, 600 mg/kg	Rat	FST, TST	28	-	-	[12]
Angelica sinensis (Apiaceae)	Ethanolic extract of roots	1 gm/kg i.g.	Rat	OFT, FST SPT	35	Fluoxetine 20mg/kg i.g.	-	[13]
Anthocephalus cadamba (Runiaceae)	Ethanolic extract of leaves	200, 400 mg/kg p.o.	Mice	FST, TST	21	Imipramine (15 mg/kg) p.o.	Triterpenes, Glycosides, Saponins, Flavonoids And Indole Alkaloids, including Isocadambine, Cadambine And Isodihydrocadambine, Cadamine	[14]
Apocynum venetum	Aqueous ethanolic extract of leaves	30, 60 & 120 mg/kg i.g.	Rat	OFT, FST, SPT	28	Fluoxetine 10 mg/kg i.g.	Rutin, Hyperoside, Isoquercitrin, Astragaloside, And Quercetin	[15]
Blighia unijugata (Sapindaceae)	Ethanolic extract of leaves	1.25, 2.5 and 5 mg/Kg) i.p.	Mice	OFT, FST, TST, Yohimbine induced Lethality test, Reserpine induced hypothermia, ptosis and diarrhea	14	Imipramine (10 mg/Kg) i.p.	-	[16]
Caesalpinia pulcherrima (Fabacaeae)	Ethanolic extract of Leaves	100, 200 and 400 mg/kg p.o.	Mice	TST, Locomotor activity by actophotometer, Sucrose Preference test	21	Fluoxetine 20mg/kg p.o.	-	[17]

						i.g.	Polyphenols, Saponins And Catechin	
Campsis grandiflora (Bignoniaceae)	Ethyl acetate extract of Flowers	40mg/kg 80mg/kg i.g.	Mice	OFT, FST, TST, Sucrose Preference Test	21	Fluoxetine 60mg/kg i.g.	-	[19]
Celastrus Paniculatus (Celastraceae)	Petroleum ether extract of seeds	50, 100 and 200 mg/kg,p.o.	Mice	FST, Sucrose Preference Test	14	Fluoxetine 20mg/kgp.o.	-	[20]
Centella asiatica (Apiaceae)	Hydroethanolic extract of plant	200, 400 and 800 mg/kg p.o	Rat	OFT,FST, EPM, T-maze Spontaneous alteration	56	Fluoxetine 10mg/kg p.o.	Triterpenoids	[21]
Chenopodium album (Chenopodiaceae)	Hydroethanolic extract of leaves	200, 400 mg/kg	Mice	FST, TST, SPT & Locomotor activity byy Actophotometer	56	Imipramine 15mg/kg	-	[22]
Cimicifuga dahurica	Ethanolic extract of rhizomes	30, 60 & 120 mg/kg	Mice	FST, TST, Resrpine induced hpothermia	42	-	-	[23]
Crataegus aronia (Rosaceae)	Aqueous extract of whole plant	10 mg/kg p.o.	Rat	-	21	Fluoxetine 2 mg/kg i.p.	Polyphenols, Flavonoids, Triterpenoids	[24]
Dipterocarpus alatus (Dipterocarpaceae)	Ethanolic extract of leaves	100mg/kg, 500mg/kg i.g.	Mice	-	21	Imipramine 20mg/kg i.g.	Quercetin, Apigenin, Procyanidin, Prodelphinidin, And Quercetin-3-Glucoside	[25]
Edgeworthia chrysantha	Ethanol extract of plant	25, 50, 100 mg/kg	Rat	OFT, SPT	21	venlafaxine 12.5 mg/kg	-	[26]
Ficus deltoidea (Moraceae)	Aqueous extract of leaves	50, 200, and 800 mg/kg p.o.	Rat	OFT, FST, SPT	28	Fluoxetine 10mg/kg p.o.	-	[27]
Fructus Akebiae (Lardizabalaceae)	Ethanolic extract of fruits	25, 50 & 100 mg/kg p.o.	Mice	FST, TST, SPT	21	Escitalopram 6.25 mg/ kg p.o.	Triterpenoid Saponins, Hederagenin	[28]
Gastrodiae Rhizoma (Orchidaceae)	Aqueous extract of rhizomes	2.5, 5, 10 g/kg p.o.	Rat	OFT, FST, TST, SPT	28	Fluoxetine 10mg/kg p.o.	-	[29]
Gentiana olivieri (Gentianaceae)	Ethanolic extract of flowering parts	200, 500, 1000 mg/kg i.g.	Rat	Sucrose preference test	21	Imipramine 10mg/kg i.m.	-	[30]
Hemerocallis citrina	Ethanolic extrct of plant	112.5, 450 mg/kg i.g.	Mice	OFT, SPT, FST	42	Fluoxetine 3mg/kg i.g.	Flavonoids, Anthraquinones, Alkaloids, Caffeoylquinic Acid Derivatives, Phenolic Acids, Triterpenoids, Phenylethanosides	[31]
Jasminum mesnyi (Oleaceae)	Petroleum Ether, Chloroform, Ethanol & Aqueous extract of	150, 300, 450, and 600 mg/kg p.o.	Mice	FST, TST	28	Imipramine 10mg/kg p.o.	Alkaloids, Glycosides, Terpenoids, Steroids, Flavonoids, Tannins, And Carbohydrate	[32]

	Stems							
Jasminum multiflorum (Oleaceae)	Petroleum Ether, Chloroform, Ethanol & Aqueous extract of Stems	150, 300, 450, and 600 mg/kg p.o.	Mice	FST, TST	28	Imipramine 10mg/kg p.o.	Alkaloids, Glycosides, Terpenoids, Steroids, Flavonoids, Tannins, And Carbohydrate	[32]
Jatropha curcas (Euphorbiaceae)	Ethanolic extract of leaves	1.25, 2.5, 5 mg/Kg i.p.	Mice	OFT, FST, TST, Reserpine induced hypothermia, ptosis and diarrhea, Yohimbine induced Lethality test,	14	Imipramine 10mg/kg i.p.	Flavonoids, Apigenin, Vitexin, Isovitexin Sterols, And Triterpenes	[33]
Lepidium meyenii (Bassicaceae)	Petroleum ether extract of dried maca powder	125, 20 & 500 mg/kg p.o.	Mice	OFT, TST	42	Fluoxetine 10 mg/kg	-	[34]
Lonicerae japonicae (Caprifoliaceae)	Ethanolic extract of leaves	1.5 g/kg i.g.	Mice	OFT, FST, TST, SPT	35	Fluoxetine 20 mg/kg i.g.	-	[35]
Momordica charantia (Curcurbitaceae)	Ethanolic extract of leaves	200, 400 mg/kg	Mice	FST, Novel suppressed feeding test	28	Fluoxetine 2.5 mg/kg	-	[36]
Morus Mesozygia (Moraceae)	Ethanolic extract of leaves	2.5, 5 or 10 mg/kg, i.p	Mice	FST, SPT	14	Imipramine 15mg/kg i.p.	Moranoline, Albafuran, Albanol, Morusin, Kuwanol, Calystegine and Hydroxymoricin	[37]
Mucuna pruriens (Leguminoseae)	hydroalcoholic extract of seeds	100 and 200 mg/kg, p.o.	Mice	FST, TST	21	Haloperidol 0.1 mg/kg, i.p. & Bromocriptine (2 mg/kg, i.p.)	L-dopa, Alkaloids minor amount of 5-hydroxytryptamine	[38]
Ormosia henryi Prain (Leguminosae)	Ethanolic extract of leaves	50, 100 & 150 mg/kg i.g.	Mice	SPT, TST, ILT	35	Fluoxetine 5.2 mg/kg i.g.	Flavonoids, Including Flavones, Flavone *C*-Glycosides, Flavone *O*-Glycosides, Isoflavones, Isoflavone *O*-Glycosides, Prenylflavones And Polymethoxyflavones	[39]
Perilla frutescens (Lamiaceae)	Aqueous extract of leaves	3, 6, 9 mg/kg p.o.	Mice	OFT, FST, TST, Sucrose Preference Test	35	Fluoxetine 20mg/kg p.o.	-	[40]
Piper betel (Piperaceae)	Extract of leaves	50mg/kg and 100mg/kg p.o.	Mice	-	35	-	-	[41]
Piper sarmentosum (Piperaceae)	Ethanolic extract of aerial parts	100, 200 mg/kg	Mice & Rat	OFT, FST, TST, SPT	28	Fluoxetine 20 mg/kg	-	[42]

Radix Polygalae	Aqueous extract of roots	0.13–1.0 g/kg for mice 0.5 and 1 g/kg for rat	Rat & Mice	SPT, FST, OFT, Novelty suppressed feeding test	28	Imipramine 10 mg/kg	Oligosaccharide Esters, Triterpene Saponins, Xanthone And Xanthone Glycosides	[43]
Rehmannia glutinosa (Scrophulariaceae)	Ethanolic extract of roots	150, 300, and 600 mg/kg p.o.	Rat	SPT	21	Fluoxetine 10mg/kg p.o.	-	[44]
Saraca asoca (Fabaceae)	Methanolic extract of Bark	100 mg/kg, p.o	Rat	FST, OFT & SPT	56	Escitalopram 10 mg/kg, p.o	Phenols, Flavonoids Such As Catechin, Epicatechin, Epigallocatechin Gallate, Tannins & Saponins.	[45]
Schisandra chinensis (Schisandraceae)	Ethanolic extract of fruits	300, 600 1200 mg/kg i.g.	Mice	OFT, FST, SPT, Y-maze test, Morris water maze test	21	Fluoxetine (10 mg/kg) i.g.	-	[46]
Sesbania grandiflora (Fabaceae)	Ethanolic extract of leaves	500 and 1000 mg/kg, p.o.	Rat & Mice	Locomotor activity by actophotometer, FST, TST, EPM, Marble burying behaviour (MBB). Reserpine induced hypothermia (RIH)	-	Fluoxetine 20 mg/kg, i.p.	Saponins, Flavonoids	[47]
Tapinanthus dodoneifolius (Loranthaceae)	Methanolic extract of plant	250, 500, 1000 mg/kg	Mice	OFT, SPT, TST	35	Fluoxetine 20mg/kg	-	[48]
Valeriana jatamansi	Ethanolic extract of roots & rhizomes	5.7, 11.4, or 22.9 mg/kg i.g.	Mice	TST, SPT	28	Fluoxetine (2.6 mg/kg) i.g.	-	[49]
Zanthoxylum armatum (Rutaceae)	Methanolic extract of leaves	100, 200 mg/kg p.o.	Mice	FST, TST, SPT	42	Imipramine 10 mg/kg p.o.	-	[50]
Ziziphus mucronata	hydromethanolic extract of	150, 300, and 600 mg/kg, p.o.	Rat	FST, SPT, EPM, Light/Dark box, Novel suppressed feeding test	30	-	-	[51]

CONCLUSION

Depression is a widespread health concern, and conventional treatments face challenges like delayed response and resistance. Medicinal plant extracts, evaluated using the CUMS model and behavioral tests, show promise as safer, multi-targeted antidepressant alternatives.

Many plant extracts tested in the CUMS model have demonstrated significant antidepressant-like effects by modulating key pathways implicated in depression, such as monoaminergic neurotransmission, HPA axis regulation, oxidative stress, neuroinflammation, and neurotrophic support via BDNF expression. Phytochemicals such as flavonoids, alkaloids, terpenoids, saponins, glycosides, polyphenols, and triterpenes have been frequently associated with these effects.

In conclusion, a growing body of evidence supports the potential of phytomedicines as adjuncts or alternatives to conventional antidepressants, offering new avenues for managing depression with improved safety and efficacy. However, further clinical studies, standardization of extracts, and elucidation of molecular targets are crucial for translating these findings into clinical practice. Integrating traditional knowledge with modern pharmacological approaches may pave the way for more holistic and effective depression treatments in the future.

ACKNOWLEDGEMENT

We would like to express our sincere gratitude to Principal Dr. S. A. Tamboli of Appasaheb Birnale College of Pharmacy, Sangli for their invaluable guidance, patience & expertise throughout this review process.

REFERENCES

1. 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.
2. Herfindal ET, Gourley DR. Textbook of Therapeutics. Drug and Disease Management, Mood disorders. Lippincott Williams & Wilkins, 2000; 7: 1203-1215.
3. Tripathi KD. Essential of Medical Pharmacology. Drugs used in Mental Illness. Antidepressant and Antianxiety Drugs. 8th edition: Jaypee Brothers Medical Publishers, 2019; 481-492.
4. Mutlu O, Gumuslu E, Ulak G, Celikyurt IK, Akar F, Bektas E, Demirtas T, Kır HM, Musul MM, Erden F. Antidepressant-Like Activity of Agomelatine in the Mouse Unpredictable Chronic Mild Stress Model. Drug Development Research, 2013; 74(3): 203-15.
5. Bakre AG, Olayemi JO, Ojo OR, Odusanya ST, Agu GA, Aderibigbe AO. Antidepressant-like effect of ethanol extract of Blighia unijugata Bak.(Sapindaceae) leaves in acute and chronic models of depression in mice. Nigerian Journal of Physiological Sciences, 2019; 31, 34(2): 191-9.
6. Dhingra D. Antidepressant-like activity of ethanol extract of leaves of Caesalpinia pulcherrima in unstressed and stressed mice. Brazilian Journal of Pharmaceutical Sciences, 2021; 26, 57: e18891.
7. Yu HC, Wu J, Zhang HX, Zhang HS, Qiao TT, Zhang JX, Zhang GL, Sui J, Li LW, Zhang LR, Lv LX. Antidepressant-like and anti-oxidative efficacy of Campsis grandiflora flower. Journal of Pharmacy and Pharmacology, 2015; 67(12): 1705-15.
8. Jiang N, Zhang BY, Dong LM, Lv JW, Lu C, Wang Q, Fan LX, Zhang HX, Pan RL, Liu XM. Antidepressant effects of dammarane sapogenins in chronic unpredictable mild stress-induced depressive mice. Phytotherapy Research, 2018; 32(6): 1023-9.
9. Xia F, Li C, Li M, Liao Y, Liu X, Si J, Chang Q, Pan R. Antidepressant activity of an aqueous extract from okra seeds. RSC advances, 2018; 8(57): 32814-22.
10. Shehu A, Magaji MG, Yau J, Ahmed A. Methanol stem bark extract of Adansonia digitata ameliorates chronic unpredictable mild stress-induced depression-like behavior: Involvement of the HPA axis, BDNF, and stress biomarkers pathways. Journal of basic and clinical physiology and pharmacology, 2019; 27, 30(3): 20180153.
11. Sharma, Ashwani, Singh, Talever, Pathak, Devender , Virmani, Tarun, Kumar, Girish, Alhalmi, Abdulsalam, Antidepressive-Like Effect of *Aegle marmelos* Leaf Extract in Chronic Unpredictable Mild Stress-Induced Depression-Like Behaviour in Rats, *BioMed Research International*, 2022; 6479953, 16: 2022.
12. Qi Y, Wu D, Wang C. Effects Of Anacyclus Pyrethrum Radix Extract On Behavioural Disorders And Activation Of Microglia In Depressive Rats Via Tlr4/Myd88/Nf-? B Signalling Pathway. Farmacia, 2024; 1, 72(2).
13. Shen J, Zhang J, Deng M, Liu Y, Hu Y, Zhang L. The antidepressant effect of Angelica sinensis extracts on chronic unpredictable mild stress-induced depression is mediated via the upregulation of the BDNF signaling pathway in rats. Evidence-Based Complementary and Alternative Medicine, 2016; 2016(1): 7434692.
14. Dhangar OP, Singh T, Chopra H, Tripathi RB, Kumar S, Garg A, Singh K, Pathak D. Antidepressant-Like Effect of Ethanolic Leaves Extract of Anthocephalus cadamba in CUMS Model of Depression in Swiss Albino Mice. Indian Journal of Pharmaceutical Education and Research, 2025; 13, 59(2s): s594-601.
15. Wu T, Li X, Li T, Cai M, Yu Z, Zhang J, Zhang Z, Zhang W, Xiang J, Cai D. Apocynum venetum leaf extract exerts antidepressant-like effects and inhibits hippocampal and cortical apoptosis of rats exposed to chronic unpredictable mild stress.

Evidence-Based Complementary and Alternative Medicine, 2018; 2018(1): 5916451.
16. Bakre AG, Olayemi JO, Ojo OR, Odusanya ST, Agu GA, Aderibigbe AO. Antidepressant-like effect of ethanol extract of Blighia unijugata Bak.(Sapindaceae) leaves in acute and chronic models of depression in mice. Nigerian Journal of Physiological Sciences, 2019; 31, 34(2): 191-9.
17. Dhingra D. Antidepressant-like activity of ethanol extract of leaves of Caesalpinia pulcherrima in unstressed and stressed mice. Brazilian Journal of Pharmaceutical Sciences, 2021; 26, 57: e18891.
18. He D, Sai X, Wang N, Li X, Wang L, Xu Y. Camellia euphlebia exerts its antidepressant-like effect via modulation of the hypothalamic-pituitary-adrenal axis and brain monoaminergic systems. Metabolic Brain Disease, 2018; 33: 301-12.
19. Yu HC, Wu J, Zhang HX, Zhang HS, Qiao TT, Zhang JX, Zhang GL, Sui J, Li LW, Zhang LR, Lv LX. Antidepressant-like and anti-oxidative efficacy of Campsis grandiflora flower. Journal of Pharmacy and Pharmacology, 2015; 67(12): 1705-15.
20. Valecha R, Dhingra D. Antidepressant-like Activity of Celastrus paniculatus Seed Oil in Mice Subjected to Chronic Unpredictable Mild Stress.
21. Jagadeesan S, Chiroma SM, Baharuldin MT, Taib CN, Amom Z, Adenan MI, Moklas MA. Centella asiatica prevents chronic unpredictable mild stress-induced behavioral changes in rats. Biomedical Research and Therapy, 2019; 29, 6(6): 3233-43.
22. Yadav SK. Antidepressant like Effects of Hydro Ethanolic Extract of Chenopodium album On Cums Induced Depression in Mice [Internet], 2021; 20.
23. Mao Z, Lv C, Qin R, Yu Y, Wang X, Lu J, Zhao Y. Antidepressant-like effects of Cimicifuga dahurica (Turcz.) Maxim. via modulation of monoamine regulatory pathways. Physiology & Behavior, 2024; 1, 284: 114616.
24. Alamri HS. Evaluation of the antidepressant-like activity of the aqueous extract of Crataegus aronia. Pharmacognosy Magazine, 2022; 18(77).
25. Daodee S, Monthakantirat O, Ruengwinitwong K, Gatenakorn K, Maneenet J, Khamphukdee C, Sekeroglu N, Chulikhit Y, Kijjoa A. Effects of the ethanol extract of Dipterocarpus alatus leaf on the unpredictable chronic mild stress-induced depression in ICR mice and its possible mechanism of action. Molecules, 2019; 18, 24(18): 3396.
26. Liu Y, Wu S, Miao S, Yan L, Huang Z, Fang G, Zhang Y, Feng Q. Effects of Edgeworthia chrysantha Lindl. Extract on BDNF and its Receptor TrkB in the Hippocampus of Depression Model Rats. Natural Product Communications, 2025; 20(1): 1934578X251314730.
27. Wang H, Moklas MA, Vidyadaran S, Baharuldin MT. Antidepressant-like effects of Ficus deltoidea aqueous extract on chronic unpredictable mild stress-treated rats. Aust J Sci Technol, 2017; 1: 21-7.
28. Zhou D, Jin H, Lin HB, Yang XM, Cheng YF, Deng FJ, Xu JP. Antidepressant effect of the extracts from Fructus Akebiae. Pharmacology Biochemistry and Behavior, 2010; 1, 94(3): 488-95.
29. Wang M, Dong W, Wang R, Xu X, Wu Y, Sun G, Sun X. Gastrodiae rhizoma water extract ameliorates hypothalamic–pituitary–adrenal axis hyperactivity and inflammation induced by chronic unpredictable mild stress in rats. BioMed research international, 2020; 2020(1): 8374614.
30. Berk A, Yılmaz İ, Abacıoğlu N, Kaymaz MB, Karaaslan MG, Savan EK. Antidepressant effect of Gentiana olivieri Griseb. in male rats exposed to chronic mild stress. Libyan Journal of Medicine, 2020; 15(1).
31. Gao S, Lu J, Gu Y, Zhang Y, Wang C, Gao F, Dai Z, Xu S, Zhang J, Yang Y, Lei H. Revealing the Mechanism of Hemerocallis citrina Baroni in Depression Treatment Through Integrated Network Pharmacology and Transcriptomic Analysis. Pharmaceuticals, 2024; 17, 17(12): 1704.
32. Garg P, Aggarwal N, Garg V, Dutt R, Singh RP, Kumar V, Chopra H, Al-Mazroua HA, Attia SM, Ahmad SF, Bin Emran T. Assessment of Antidepressant Activity of Stem of Jasminum multiflorum Andrews and Jasminum mesnyi Hance by Modulating Neurochemicals and Reducing Oxidative Stress. Journal of Biological Regulators and Homeostatic Agents, 2024; 1, 38(2): 1649-61.
33. Bakre AG, Odusanya ST, Olowoparija SF, Ojo OR, Olayemi JO, Aderibigbe AO. Behavioral and biochemical evidences for antidepressant activity of ethanol extract of Jatropha curcas in mice subjected to chronic unpredictable mild stress. J Biol Nat, 2020; 11: 1-0.
34. Ai Z, Cheng AF, Yu YT, Yu LJ, Jin W. Antidepressant-like behavioral, anatomical, and biochemical effects of petroleum ether extract from maca (Lepidium meyenii) in mice exposed to chronic unpredictable mild stress. Journal of medicinal food, 2014; 1, 17(5): 535-42.
35. Qin L, Wang J, Wu X, Song L, Zhang Y, Gong M, Wang Y, Li B. Antidepressant effects of 70% ethanolic extract of Lonicerae japonicae flos and it contained chlorogenic acid via upregulation of BDNF-TrkB pathway in the hippocampus of mice. Brain Research Bulletin, 2023; 1, 204: 110796.
36. Kristiyani A, Ikawati Z, Gani AP, Sofro ZM. Antidepressant Activity Of 80% Bitter Melon-Leaf Ethanol Extract (Momordica Charantia L.) And?-Sitosterol Compound In Vivo. Jurnal Ners, 2025; 9(1): 44-52.
37. Aderibigbe AO, Sowunmi AA, Usman Y, Olonode E. Behavioral and Biochemical Evidences of Antidepressant Activity of Ethanolic Extract of Morus Mesozygia Leaves in Mice Subjected to Chronic Unpredictable Mild Stress.
38. Rana DG, Galani VJ. Dopamine mediated antidepressant effect of Mucuna pruriens seeds in various experimental models of depression. AYU (An International Quarterly Journal of Research in Ayurveda), 2014; 1, 35(1): 90-7.

39. Lu Y, Zhu S, He Y, Peng C, Wang Z, Tang Q. Phytochemical profile and antidepressant effect of Ormosia henryi Prain leaf ethanol extract. International Journal of Molecular Sciences, 2019; 10, 20(14): 3396.
40. Wei-Wei JI, Rui-Peng LI, Meng LI, Shu-Yuan WA, Xing-Xing NI, Wei LI, Lu YA, Yang WA, Qiang FU, Shi-Ping MA. Antidepressant-like effect of essential oil of Perilla frutescens in a chronic, unpredictable, mild stress-induced depression model mice. Chinese journal of natural medicines, 2014; 1, 12(10): 753-9.
41. Chowdhury SR, Ghosh S, Chatterjee S, Murtuja S, Rakshit G, Basu B, Prajapati BG, Ali N. Antidepressant-Like Effects of Hydroxychavicol Enriched Piper betel L. Leaf Extract in Chronic Mild Stress-Induced Rodent Models and Possible Mechanism (s) of Action Involved. Chemistry & Biodiversity, e202402842.
42. Li Q, Qu FL, Gao Y, Jiang YP, Rahman K, Lee KH, Han T, Qin LP. Piper sarmentosum Roxb. produces antidepressant-like effects in rodents, associated with activation of the CREB-BDNF-ERK signaling pathway and reversal of HPA axis hyperactivity. Journal of Ethnopharmacology, 2017; 6, 199: 9-19.
43. Zhou Y, Yan M, Pan R, Wang Z, Tao X, Li C, Xia T, Liu X, Chang Q. Radix Polygalae extract exerts antidepressant effects in behavioral despair mice and chronic restraint stress-induced rats probably by promoting autophagy and inhibiting neuroinflammation. Journal of ethnopharmacology, 2021; 30, 265: 113317.
44. Wang JM, Pei LX, Zhang YY, Cheng YX, Niu CL, Cui Y, Feng WS, Wang GF. Ethanol extract of Rehmannia glutinosa exerts antidepressant-like effects on a rat chronic unpredictable mild stress model by involving monoamines and BDNF. Metabolic Brain Disease, 2018; 33: 885-92.
45. Gill M, Kinra M, Rai A, Chamallamudi MR, Kumar N. Evaluation of antidepressant activity of methanolic extract of Saraca asoca bark in a chronic unpredictable mild stress model. Neuroreport, 2018; 17, 29(2): 134-40.
46. Yan T, He B, Wan S, Xu M, Yang H, Xiao F, Bi K, Jia Y. Antidepressant-like effects and cognitive enhancement of Schisandra chinensis in chronic unpredictable mild stress mice and its related mechanism. Scientific Reports, 2017; 31, 7(1): 6903.
47. Bhatt S, Rajangam J, Rajitha K. Neuropharmacological evaluation of Sesbania grandiflora (L.) Pers. leaves in preclinical models of depression and co-morbid anxiety. FOR HEALTHCARE PROFESSIONALS: SCOPE AND OPPORTUNITIES, 2020(3); 65.
48. Bello N, Shehu A, Maje Im, Magaji Mg. Antidepressant Effect of Methanol Extract of Tapinanthus Dodoneifolius (Dc) Danser Involves Neutrotrophic And Neuroendocrine Systems Following Chronic Stress In Mice.
49. Wang L, Sun Y, Zhao T, Li Y, Zhao X, Zhang L, Wu L, Zhang L, Zhang T, Wei G, Altamirano A. Antidepressant effects and mechanisms of the total iridoids of Valeriana jatamansi on the brain-gut axis. Planta medica, 2020; 86(03): 172-9.
50. Yadav CK, Poudel K, Mehta R, Shrivastava AK. Anti-depressant activity of the leaves of Zanthoxylum armatum on Swiss albino mice. Journal of Universal College of Medical Sciences, 2020; 31, 8(02): 46-50.
51. Wado EK, Kubicki M, Ngatanko AH, Blondelle KD, Roland RN, Balbine K, Lamshoeft M, Assongalem AE, Foyet HS. Anxiolytic and antidepressant effects of Ziziphus mucronata hydromethanolic extract in male rats exposed to unpredictable chronic mild stress: Possible mechanisms of actions. Journal of ethnopharmacology, 2020; 5, 260: 112987.