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REVIEW ON NATURAL AGENTS USED AS ANTIDEPRESSANT

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ABSTRACT

Depression is a mood disorder characterized by a wide range of symptoms that result in psychomotor and cognitive impairments. Depression follows loss of pleasure or interest, feeling of guilt, decreased energy and low self-worth. Chemical and synthetic drugs available to treat depression causes many adverse effects and may lead to complete recovery in only 50% of patients. At the same time, medicinal plants have been reported to exert optimal pharmacological effects in treating depression in different animals. Most medicinal plants exerted antidepressant effects through synaptic regulation of serotonin, noradrenaline, and dopamine, regulating activity of hypothalamic-pituitary-adrenal axis, reinforcing anti-oxidant defense system, and decreasing inflammatory mediators. The medicinal plants and their active compounds can relieve depression through different pathways and hence can act as antidepressants agents.

KEYWORDS: Antidepressant, CNS disorder, Depression, Medicinal plants, Neurotransmitters.

INTRODUCTION

Depression is a mood disorder, characterized by symptoms like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation or agitation, change in appetite and/or sleep, melancholia, suicidal thoughts, etc.[1] According to the World Health Organisation 2020, 322 million people worldwide suffer from depression. 75% of people suffering from a mental disorder receive no treatment in developing countries. Over 34 million US residents 65 and above aged are currently suffering from depression. 20% of people suffer from at least one depressive episode before becoming adults.[2] Prevalence of depressive disorders was highest in Tamil Nadu (loss of 836 years per 1 lakh population), Kerala (loss of 641 years), Goa (loss of 626 years) and Telangana (loss of 756years) in the high SDI State group and Andhra Pradesh (loss of 793 years) in the middle SDI State group.[3]

The proportion of the global population with depression in 2015 is estimated to be 4.4%. Depression is more common among females (5.1%) than males (3.6%). Prevalence rates vary by age, peaking in older adulthood (above 7.5% among females aged 55-74 years and above 5.5% among males). Depression occur in children and adolescents below the age of 15 years but at a lower level than older age groups.[4] The different brain regions may mediate variety of symptoms of depression as they regulate emotions, mood and neural circuitry. The malfunctioning of the hypothalamus region of the brain has been associated with very less or too much sleep, disinterest in sex and other activities of enjoyment.

Depression has three main forms such as

i. Psychotic depression characterised by severe depression.
ii. Seasonal Affective Disorder (SAD) concerning specially the winter months with less sunlight
iii. Postpartum depression characterised by perturbations in the levels of hormones and physical features after child birth.[5]

Types of depression

- **Major depression:** In this type it shows symptoms of depression nearly every day for at least 2 weeks that interfere with your ability to work, sleep, study, eat, and enjoy life. An episode can occur only once in a person's lifetime, but more often, a person has several episodes.

- **Persistent depressive disorder (dysthymia):** In this type it shows symptoms of depression that last for at least 2 years. A person diagnosed with this form of depression may have episodes of major depression along with periods of less severe symptoms.[1]
- **Perinatal depression:** Women with perinatal depression experience full-blown major depression during pregnancy or even after delivery (postpartum depression).
- **Seasonal affective disorder (SAD):** In this type of depression that comes and goes with the seasons, typically starting in the late fall and early winter and going away during the spring and summer.
- **Psychotic depression:** In this type of depression occurs when a person has severe depression plus some form of psychosis, such as having disturbing false fixed beliefs (delusions) or hearing or seeing upsetting things that others cannot hear or see (hallucinations).[1,5]

Signs and Symptoms of depression

- Persistent sad, anxious, or "empty" mood
- Feelings of hopelessness.
- Feelings of guilt, worthlessness, or helplessness
- Loss of interest or pleasure in hobbies or activities
- Decreased energy, fatigue, or being "slowed down"
- Difficulty concentrating, remembering, or making decisions
- Difficulty sleeping, early-morning awakening, or oversleeping
- Appetite and/or weight changes
- Thoughts of death or suicide or suicide attempts
- Restlessness or irritability
- Aches or pains, headaches, cramps, or digestive problems without a clear physical cause and/or that do not ease even with treatment.[6]

Mechanism of depression

Chemical transmission requires several steps including synthesis of the neurotransmitters, their storage in secretory vesicles, and their regulated release into the synaptic cleft between pre- and postsynaptic neurones, but also the termination of neurotransmitter action and the induction of the final cellular responses via different steps in the signal transduction cascade.

The initial step of synthesis is the facilitated transport of amino acids from blood to the brain, where precursors are converted via enzymatic reactions into transmitters, which are stored in synaptic vesicles, and finally released into the synaptic cleft by a Ca2+-dependent process. The rate of neurotransmitter release is dependent on the firing rate of the neurones, which means that conditions or drugs that alter the firing rate modify the release of the transmitter. A further important regulatory mechanism of release involves the somatodendritic autoreceptors, since binding of the released transmitter molecules leads to reduced synthesis or further release from the presynapse. The synaptic effects are terminated by binding of the transmitters to specific transporter proteins and reuptake into the presynapse, where they are metabolized by enzymes, for example, monoamine oxidase (MAO), or stored once again in the vesicles.[7]

Monoamine hypothesis

The main symptoms of depression are due to a functional deficiency of the brain monoaminergic transmitters norepinephrine (NE), 5-HT, and/or dopamine (DA), whereas mania is caused by functional excess of monoamines at synapses in the brain. Monoaminergic systems are responsible for many behavioural symptoms, such as mood, vigilance, motivation, fatigue, and psychomotor agitation or retardation. Abnormal function and the behavioural consequences of either depression or the manic state may arise from altered synthesis, storage, or release of the neurotransmitters, as well as from disturbed sensitivity of their receptors or subcellular messenger functions.[8]

Evaluation of antidepressant activity

a. Forced swim test

Forced swim test was proposed by Porsolt et. al., 1978. Mice or Rat are individually forced to swim in an open cylindrical container (diameter 15 cm, height 20 cm), filled with water (25±1ºC) to the depth of 15 cm. Each animal will be subjected to a pre-test session (15 minutes) in the vessel 24 hours before the swimming test which last about 6 minutes. The immobility time were observed for each animal. Animal were considered as immobile if they made no further attempt to escape, except the movement necessary to keep their head above water.[9]

b. Tail suspension test

Tail suspension method was proposed by Steru et al., 1985. Mice or Rats are used. Each animal was individually suspended on the edge of the table, 35cm above the floor, with the

help of adhesive tape place approximately 2cm from the tip of the tail. The total duration of immobility 3==induce by tail suspension were recorded for 6 minutes. Animal were considered as immobile when they do not show any body movement and remain completely motionless.[10]

c. Open-Field Test (OFT)

Open field test (OFT) was proposed by Dews, 1952. Animals were placed individually in open field apparatus after dosing. The open–field apparatus consists of a wooden arena (64cm x 64cm and 40cm high). The floor of the wooden arena is divide into 16 equal squares and mark by black lines. The mice were placed individually in the centre of the arena and allow to explore freely. The number of squares cross by the animal and the number of rearings behavior were recorded during a test period of 5min. The test will be carried out at room temperature of 27 ± 2°C in a noise and light controlled room.[11]

Preclinical studies

Sl.no	Author	Treatment	Plants	Evaluation methods	Effect
1.	Purna chander et al[12]	Animal (Sprague Dawley rat)	 *Barleria buxifolia*	Forced swim test	Decrease immobility duration
2.	Bikomo et al[13]	Animal (Sprague Dawley rats)	 *Annona muricata*	Forced Swim test Open field Test	Decrease immobility duration
3.	Chaitra SR et al[14]	Animal (Wistar albino rat)	 *Psidium guajava*	Forced swim test Tail suspension test	Decrease immobility duration
4.	Prathvi Shetty et al[15]	Animal (Swiss albino mice)	 *Bauhinia purpurea*	Forced swim test Tail suspension test	Decrease immobility duration
5.	Ibrahim et al[16]	Animal (Swiss albino mice)	 *Leptadenia hastata*	Forced swim test Tail suspension test	Decrease immobility duration
6.	Rout S et al[17]	Animal (Swiss albino mice)	 *Musa x paradisiaca*	Forced swim test Tail suspension test	Decrease immobility duration

7.	Udyavar et al[18]	Animal (Swiss albino mice)	 *Mimosa pudica*	Forced swim test Tail suspension test	Decrease immobility duration
8.	Kudagi et al[19]	Animal (Swiss albino mice)	 *Prosopis cineraria*	Tail suspension test	Decrease immobility duration
9.	Rahman et al[20]	Animal (Swiss albino mice)	 *Sesamum indicum*	Tail suspension test Forced swim test Open field test	Decrease immobility duration
10.	Aslam Pathan[21]	Animal (Swiss albino mice)	 *Coriandrum sativum*	Forced Swim test Locomotor activity	Decrease immobility duration
11.	Kumar Yadav et al[22]	Animal (Swiss albino mice)	 *Zanthoxylum armatum*	Forced swim test Tail suspension test	Decrease immobility duration
12.	Bakou Niangoran Francois et al[23]	Animal (Swiss albino mice)	 *Griffonia simplicifolia*	Forced swim test Tail suspension test	Decrease immobility duration
12.	Fekadu et al[24]	Animal (Swiss albino mice)	 *Rosa abyssinica*	Tail suspension test Forced swim test Open field test	Decrease immobility duration
13.	Jamwal Neetu Singh et al[25]	Animal (Swiss albino mice)	 *Foeniculum vulgare*	Forced swim test	Decrease immobility duration
14.	Parle Milind et al[26]	Animal (Swiss albino mice)	 *Carica papaya*	Tail suspension test Forced swim test	Decrease immobility duration
15.	Kameshwaran et al[27]	Animal (Swiss albino mice)	 *Tecoma stans* flower	Tail suspension test Despair swim test	Decrease immobility duration

16.	Tiwari Prashant et al[28]	Animal Swiss albino mice)	 *Zingiber officinale*	Forced swim test Tail suspension test	Decrease immobility duration
17.	Lalremruati et al[29]	Animal (Swiss albino mice)	 *Colocasia affinis*	Forced swim test Tail suspension test	Decrease immobility duration
18.	Mythili et al[30]	Animal (Swiss albino mice)	 *Justicia gendarussa*	Forced swim test	Decrease immobility duration
19.	Prabhakar Adake et al[31]	Animal (Swiss albino mice)	 *Boswellia serrata*	Forced swim test	Decrease immobility duration

Medicinal plants (Leaves) used as antidepressants

***Barleria buxifolia* linn**

Studies investigated by **Purna Chandra *et.al* (2013)** showed the antidepressant activity of *Barleria buxifolia* Linn[12] leaves which belongs to the family Acanthaceae. Forced swim test is widely used method for assessing antidepressant activity. The oral administration of aqueous extract of *Barleria buxifolia* at the dose of 100 and 200mg/kg showed a significant decrease in the immobility duration as compared with Imipramine. Thus the study concluded that the aqueous leaf extract of *Barleria buxifolia* produces significant antidepressant activity.

Annona muricata

Studies evaluated by **Bikomo *et al* (2017)** showed the antidepressant activity of *Annona muricata*[13] is widely employed in herbal medicine. Ethanol extract of *Annona muricata* caused a significant reduction in immobility time and increased swimming time, which demonstrated antidepressant-like effect. The extract significantly decreased locomotive activity alone and in combination with imipramine. The increase in active behaviour (swimming) and decrease in immobility observed in the FST was not due to an increase in locomotors activity (as shown in the OFT). Therefore, the antidepressant-like effect of the extract is not related to a psycho stimulant effect.

Psidium guajava

Antidepressant activity of aqueous extract of *Psidium guajava*[14] were studied by **Chaitra *et al* (2019)**. *Psidium guajava* is commonly known as guava. *Psidium guajava* leaf aqueous extract 100mg/kg and 200mg/kg body weight possess significant antidepressant activity in Wistar albino rats. Aqueous extract of *Psidium guajava* 200mg/kg dose showed significant activity compared to 100mg/kg dose. This reveals that exact mechanism which might be responsible for the antidepressant activity.

Neurobehavioral activities of ethanolic extract of *Psidium guajava*[32] Linn leaves in mice model were investigated by **Biswas *et al* (2021).** Phytochemical constituents present in ethanolic extract of *Psidium guajava* leaves are steroids, flavonoids, alkaloids, glycosides, tannins, terpenoids, carbohydrates and proteins. Antidepressant activity were studied by using Forced swim test and Tail suspension test of dose 200mg/kg and 400mg/kg. Aqueous extract of *Psidium guajava* leaves showed the significant decrease of immobility time in FST and TST was found at dose of 400mg/kg but not at dose of 200mg/kg as compared with Imipramine. This reveals that aqueous extract of *Psidium guajava* leaves produce antidepressant activity at dose 400mg/kg.

Bauhinia purpurea

Studied evaluated by **Prathvi Shetty *et al* (2017)** showed the antidepressant activity of *Bauhinia purpurea*[15] commonly known as purple orchid tree. Extract of *Bauhinia purpurea* leaves shows phytoconstituents such as flavanoids, saponins, tannins and phytosterols. These phytoconstituents also possess neuroprotective effects. Ethanolic extract of *Bauhinia Purpurea* leaves produces antidepressant like activity in Swiss Albino mice.

Prosopis cineraria

Antidepressant activity of aqueous extract of *Prosopis cineraria*[16] were studied by **Kudagi *et al* (2018)**. Prosopis cineraria is a leguminous multipurpose tree. Antidepressant activity were evaluated by using Tail suspension test. The aqueous extract of *Prosopis cineraria* leaves possesses antidepressant effects which might occur due to interaction with noradrenergic and serotonergic systems.

Leptadenia hastate

Antidepressant activity of methanol leaves extract of *Leptadenia hastate*[17] in mice were investigated by **Ibrahim *et al* (2019)**. The phytochemical constituents of the methanol leaves

extract of *Leptadenia hastata* have showed the presence of secondary metabolites such as alkaloids, flavonoids, glycosides, tannins, saponins and steroid. The antidepressant like effects of LHME were evaluated by the method like TST and FST. The methanolic leaves extract of *Leptadenia hastata* (10, 100 and 1000mg/kg) showed that significant decrease the duration of immobility time in TST and FST. Thus the antidepressant like effect exhibited by *Leptadenia hastata* plant may be due to phytochemical constituents found present in the plant.

Musa x paradisiaca

Rout S *et al* (2019) investigate the antidepressant activity of the methanolic extract of the leaves of *Musa x paradisiaca*[18] Linn. In this study the extracts like Methanol extract *Musa x paradisiaca* Linn (MEMPL) and Aqueous extract *Musa x paradisiaca* Linn (AEMPL) of dose 200 and 400mg/kg showed decrease in immobility period in both the models like TST and FST. The phytochemicals present in the plant extract may be monoaminergic transmission there by producing antidepressant effects. This conclude that flavonoids may be responsible for antidepressant activity in experimental animal models.

Mimosa pudic

Antidepressant activity of ethanolic extract of *Mimosa pudica*[19] (EEMP) in Swiss albino mice were evaluated by **Udyavar *et al* (2020)**. In this study EEMP dose selected for evaluating antidepressant activity are 100, 200, 400mg/kg and evaluation carried out on 1st and 10th day of treatment. The result obtained in this study suggests that EEMP produce antidepressant activity due to the presence of some active constituent like alkaloids, flavonoids and tannins in the extract.

Medicinal plants (Seed) used as antidepressants

Sesanum indicum

Sesamum indicum[20] has antioxidant, antitumor, antihypertensive, neuroprotective, hypoglycemic, antimicrobial, anticonvulsant and wound healing activity. The methanolic extract of the seeds of *Sesamum indicum* were investigated by **Rahman *et al* (2019).** In this study methanolic extract of *Sesamum indicum* seeds possesses a significant antidepressant-like activity. This is indicated by the decrease in the duration of immobility in behavioural despair based models of depression. The antidepressant-like effect of the methanol fractions of the extract as observed in the TST and FST were found statistically significant. The

outcome of OFT indicates that effect on locomotor activity at all extract doses, the antidepressant- like activity observed is not caused by a non-specific motor stimulation.

Coriandrum sativum

Coriandrum sativum[21] seeds used as a traditional medicine to relieve stress and other neurological disease conditions. **Aslam Pathan *et.al* (2015)** evaluated the antidepressant activity in Seeds of *Coriandrum sativum* ethanolic extract. In this study the antidepressant activity was evaluated by using the method forced swim test at doses of 100 and 200 mg/kg. Distilled water and Imipramine (10mg/kg) were act as negative and positive control groups for screening antidepressant effect. Distilled water and diazepam (3mg/kg) were act as negative and positive control groups for screening anxiolytic effect. The results of this study reveals that traditional usage of seeds of *Coriandrum sativum* shows antidepressant and anxiolytic effect.

Zanthoxylum armatum

Zanthoxylum armatum[22] is also known for variety of its medicinal properties. Antidepressant activity of seeds of *Zanthoxylum armatum* on Swiss albino mice was studied by **Chandrajeet Kumar Yadav *et.al* (2020).** In this study antidepressant activity of Seeds extract of *Zanthoxylum armatum* was investigated by using the method forced swim test and tail suspension test on swiss albino mice. The anti-depressant activity of the seeds of *Zanthoxylum armatum* was assessed using Chronic Unpredictable Mild-Stress (CUMS) induced depression in mice. The animals were treated with the Methanolic extract of seeds of *Zanthoxylum armatum* orally at two doses of 100, 200 mg/kg body weight for eight days after (CUMS) induced depression in mice. These results demonstrated that Methanolic extract of *Zanthoxylum armatum* has anti-depressant potential.

Griffonia simplicifolia

Bakou Niangoran Francois *et al* (2020) evaluate the acute and chronic behavioral and antidepressant effects of aqueous extracts of *Griffonia simplicifolia*[23] **(GS) leaves** in standardized rats models of depression. In this study, the significant reduction in the immobility time observed in the FST and TST following the acute and chronic administration of GS 100mg/kg, 200 mg/kg and 400 mg/kg suggests the antidepressant action of GS. The extract to reduce the immobility time as a function of the increase in the dose may be due to a reduction in the synthesis of corticosteroid hormone since the active molecules exert a predominant noradrenergic effect by increasing the climbing time and a serotonergic effect

by increasing swimming time. Thus this study suggests that aqueous extracts of GS may possess an antidepressant activity. The preliminary pharmacological screening with acute dosing exhibited the antidepressant activity of GS, but its antidepressant activity was more enhanced after repeated dosing. In comparison with the acute studies, chronic dose studies displayed a significant antidepressant manifestation in the behavioural patterns when compared to the vehicle controls. This effect possesses more significantly pronounced in animals treated with GS at a dose of 200 and 400mg/kg/day.

Medicinal plants (Fruit) used as antidepressants

Rosa abyssinica

Rosa abyssinica[24] used for the treatment of rheumatic pain, hypertension, scabies, cough, glandular tuberculosis and diabetes. The antidepressant activity of Crude extract of *Rosa abyssinica* was studied by **Eugidawork *et.al* (2016).** Fruits of *Rosa abyssinica* possesses a notable antidepressant-like activity by using the method Forced swim test. Open field test indicates that the plant has no significant effect on locomotor activity suggesting that the antidepressant-like activity observed is not caused by a non-specific motor stimulation.

Foeniculum vulgare

Antidepressant activity of *Foeniculum vulgare*[25] fruits was studied by **Jamwal Neetu Singh *et.al* (2013)**. In this study *Foeniculum vulgare* act as a monoamine inhibitor because it increases the level of norepinephrine, serotonin and dopamine in brain. The methanolic extract of *Foeniculum vulgare* possess significant antidepressant activity due to its reduction in the immobility period in FST and reduction in the duration of catalepsy in haloperidol induced catalepsy. Thus the study concluded as Methanolic extract of *Foeniculum vulgare* produce antidepressant activity.

Carica papaya

Antidepressant potential of *Carica papaya* fruit in rodents was studied by **Parle Milind *et al* (2011).** *Carica papaya* L[26] is commonly known as Papaya. Fresh *Carica papaya* pulp reduced the immobility duration of mice significantly in TST and diminished the despair behaviour induced by forced swimming in mice. Mechanism of action for the beneficial effect of Papita in depression appears to be related to its MAO inhibitory activity, antioxidant property.

Medicinal plants (Flower) used as antidepressants

Tecoma stans

Antidepressant activity of methanol and aqueous extract of *Tecoma stans*[27] was studied by **Kameshwaran *et al* (2014).** *Tecoma stans* plants have therapeutic bioactive compounds. The phytochemical constituents in these extract shows the presence of glycosides, tannins, flavonoids, alkaloids, saponins, and coumarins in the raw leaves and extract can have synergistic effect influencing the efficacy of the extract to produce a desired or intended pharmacological effect reported. Thus the study reveals that antidepressant activity of *Tecoma stans* is mediated through dopaminergic, adrenergic and serotonergic mechanisms.

Medicinal plants (Rhizome) used as antidepressants

Zingiber officinale

Antidepressant activity of hydroalcoholic extract of *Zingiber officinale* was evaluated by **Tiwari Prashant *et al* (2012).** *Zingiber officinale*[28] is one of the most widely used species of the ginger family Zingiberaceae. The plant extract *Zingiber officinale* shows a significant antidepressant activity in Tail suspension test and forced swim test models of depression. *Zingiber officinale* significantly reduces the immobility period in both TST and FST.

Medicinal plants (Spadix) used as antidepressants

Colocasia affinis

Antidepressant activity of *Colocasia affinis*[29] spadix was studied by **Lalremruti *et al* (2018).** *Colocasia affinis* has secondary metabolites such as fats and fixed oils, steroids and triterpenoids in petroleum ether extract, steroids and triterpenoids in chloroform extract, flavonoids and tannins in methanol extract and carbohydrates in the aqueous extract. An antidepressant activity was performed on the methanolic extract of the plant at two different doses using force swim test and tail suspension test on an experimental animal model. Imipramine was used as a standard drug for the study. The result indicates that the methanolic extract shows antidepressant effect as similar to that of Imipramine.

Medicinal plants (Aerial part) used as antidepressants

Justicia gendarussa

Mythili *et al* (2017) studied the antidepressant activity of ethanolic extract of *Justicia gendarussa*.[30] *Justica gendarussa* is an herbal plant which has several therapeutic effects. In this study the phytochemical screening shows the presence of Flavonoids, Alkaloids and Glycoside which may possess antidepressant effect. The ethanolic extract (500 mg/kg) was

found to be effective and it exhibited activity similar to that of the conventional drug imipramine, whereas 250 mg/kg dose showed higher activity with significantly increased swimming time and decreased immobility time than 500 mg/kg of ethanolic extract and imipramine. Thus the study proves the potential anti-depressant activity of *Justicia gendarussa* in a dose dependent manner. Thus *Justicia gendarussa* has the potential to be used as an adjuvant in the treatment of depressant and other mood disorder.

Medicinal plants (Gum resin) used as antidepressants

Bosewellia serrata

Antidepressant activity of *Boswellia serrata*[31] was studied by **Prabhakar Adake et al (2013).** *Bosewellia serrata* gum has been mentioned in the ancient Ayurvedic texts- Sushruta Samhita and Charaka Samhita. In this study *Boswellia serrata* has significant antidepressant activity in experimental animal model (Forced swim test). Three different doses of *Boswellia serrata* (50mg/kg, 100mg/kg and 200mg/kg) evaluated for its antidepressant activity using Forced Swim Test (FST) model. *Boswellia serrata* in a dose of 100mg/kg significantly reduced immobility period in FST compared to control group. 50mg/kg and 200mg/kg dose of *Boswellia serrata* failed to reduce immobility period compared to control group. This shows that *Boswellia serrata* has significant antidepressant activity in a dose of 100mg/kg. Hence can be an alternative to conventional antidepressant drugs.

CONCLUSION

The collection of herbal plants showing the antidepressant activity were tabulated from the various journals and were reported above as we can conclude that herbal plants are very rich source of substance which are responsible for increasing the antidepressant activity.

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