Original Article

A REVIEW ON ANTIDEPRESSANT EFFECT OF HERBAL DRUGS

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Abstract

Depression is a psychiatric illness, which affects the patient's mood, behaviour and thoughts. Several number of studies are exists about depression which state that depression is a mental health disorder characterised by depressed mood or loss of interest in activities. A variety of conventional drugs are in practice for the treatment of depression. But their side effects and drug interactions restricts their clinical utility. On the other hand, herbal drugs are now globally used due to their applicability and therapeutic efficacy with minimum or low side effects. This study is aimed to summarize the possible biological actions of some herbal drugs to further understand their beneficial health effects against depression, anxiety, and various neurological disorders. A literature survey was conducted to summarize the therapeutic benefits of several medicinal herbs against depression and describe their detailed mechanisms. The current data from recent studies showed that numerous herbal drugs are available which are effective against depression and other related disorders. These were found safer than synthetic drugs. The use of herbal drugs is an effective alternative option for the treatment of depression where the synthetic or conventional drugs are not applicable due to their severe side effects and inaccessibility. Though, clinical studies are required to support the safety and efficacy of herbal drugs in the treatment of depression.

Keywords – Herbal Drugs, Depression, Antidepressant Effect, Psychiatric Illness

❖ INTRODUCTION

Mania and depression are two extremes of affective illnesses, both of which refer to a pathological alteration in mood. Sad & depressed mood, lack of interest & pleasure, poor energy, worthlessness, guilt, psychomotor slowness or agitation, change in appetite and sleep, melancholia, suicidal thoughts, and other symptoms describe major which mood swings cycle from mania to depression over time. The mood shift could be psychotic in nature, with delusional thinking, or it could happen on its own, causing anxiety. Pathological anxiety, on the other hand, can lead to depression. Anxiety and sadness are currently the most common psychiatric disorders [1]. Depression is a common mental disorder. Globally, it is estimated that 5.0% of adults suffer from depression. Depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease. Antidepressants are the drugs used to treat people suffering from depressive disorders. They restore neurotransmitter chemical imbalances in the brain, which are thought to be the cause of mood and behaviour abnormalities. Epidemiological study shows that depression is the most common mental disorder in man. Up to 4% of men and 8% of women suffers from a clinically significant depressive disorder [2]. Few medications can help people with depression to feel better. Almost all antidepressants detect monoaminergic transmission in the brain in some way, and many of them have additional qualities as well. Over the last three decades, a wide number of antidepressants have become available, each having a different action on biogenic amine reuptake/metabolism and pre/post-junctionalaminergic /cholinergic receptors, making a clear classification impossible. Antidepressants can be used to treat a variety of mental illnesses, such as social anxiety disorder, anxiety disorders, and dysthymia (mild chronic depression) [3].

❖ TYPES OF ANTIDEPRESSANTS

There are roughly thirty different types of antidepressants, according to the Royal College of Psychiatrists in England, which can be grouped into five categories:

1. Monoamine Oxidase Inhibitors (MAOIs)

Antidepressants that suppress the action of monoamine oxidase, a brain enzyme, are known as monoamine oxidase inhibitors. Monoamine oxidase aids in the breakdown of neurotransmitters like serotonin. If less serotonin is broken down, the patient's moods should be more stable and anxiety should be reduced. Because MAOIs interact with a large number of other drugs and foods, doctors typically use them if SSRIs haven't worked. MAOIs have the following possible side

effects: blurred vision, rash, seizures, edema, weight loss, weight gain, sexual dysfunction, diarrhoea, nausea, constipation, anxiety, insomnia, drowsiness, headache, dizziness, arrhythmia, fainting, feeling faint when standing up (postural hypotension), and hypertension.

Examples: - Phenelzine (Nardil), Tranylcypromine (Parnate), Isocarboxazid (Marplan) and Selegiline (EMSAM,Eldepryl).

2. Noradrenaline and Specific Serotoninergic Antidepressants (NASSAs)

These are a class of compounds which are used in the treatment of anxiety disorders, some personality disorders, and depression. Constipation, dry mouth, weight gain, drowsiness, sedation, blurred vision, and dizziness are all possible side effects of NASSAs. Seizures, white blood cell decrease, fainting, and allergic responses are among the more significant side effects.

Examples: - Mianserin (Tolvon) and Mirtazapine (Remeron, Avanza, Zispin).

3. Serotonin and Noradrenaline Reuptake Inhibitors (SANRIs)

SANRIs are a class of medications that are used to treat serious depression, mood disorders, and possibly, but less usually, ADHD (attention deficit hyperactivity disorder), obsessive-compulsive disorder, and obsessive-compulsive personality disorder. Obsessive-compulsive disorder, anxiety disorders, menopausal symptoms, fibromyalgia, and persistent neuropathic pain are all examples of compulsive disorders. Serotonin and norepinephrine, two neurotransmitters in the brain, are increased by SANRIs.

Examples: - Duloxetine (Cymbalta), Venlafaxine (Effexor) and Desvenlafaxine (Pristig).

4. Selective Serotonin Reuptake Inhibitors(SSRIs)

The most often prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs). According to experts, SSRIs are not only helpful at treating depression, but they also have fewer side effects than other drugs. SSRIs help the brain cells receive and send messages by blocking serotonin reuptake. This leads in better and more stable moods. They are referred to be "selective" since they appear to influence only serotonin and not other neurotransmitters. SSRIs and SANRIs may have the following side effects: hypoglycaemia, low sodium in body, nausea, rash, dry mouth, constipation, diarrhoea, weight loss, sweating, tremor, sedation, sexual dysfunction, insomnia, headache, dizziness, anxiety, agitation, and abnormal thinking.

Examples: - Italopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac, Sarafem), Fluvoxamine (Luvox), Paroxetine (Paxil) and Sertraline (Zoloft).

5. Tricyclic Antidepressants (Tricyclics)

Tricyclics get their name from the fact that their chemical structure has three rings. This class of drugs is used to treat depression, as well as some types of anxiety, fibromyalgia, and chronic pain management. Seizures, sleeplessness, anxiety, arrhythmia, hypertension, rash, nausea, vomiting, abdominal cramps, weight loss, constipation, urine retention, elevated eye pressure, and sexual dysfunction are all possible side effects of tricyclics.

Examples: - Amitriptyline (Elavil), Amoxapine Clomipramine (Anafranil), Desipramine (Norpramin), Doxepin (Sinequan), Imipramine (Tofrani), Nortriptyline (Pamelor), Protriptyline (Vivactil) and Trimipramine (Sumontil).

Antidepressants differ in how they alter neurotransmitters, how they are administered, and what side effects or drug interactions they cause. One patient may not respond to one type of antidepressant but benefit from another, while another with a similar disease may respond in the opposite direction [4].

❖ HIGHLIGHT ON CONSUMPTION OF ANTIDEPRESSANT IN LAST DECADES

Antidepressants were used by 13.3 million people in the United States in 1996. By 2010, the population had risen to 23.3 million. Researchers from Columbia University Medical Center, New York State Psychiatric Institute, and University of Pennsylvania said rates among racial and ethnic minorities remained low.

They believe antidepressant usage has become more common because:

a. There has been a shift in the way people think about the necessity for mental health treatment.
b. The use of public awareness campaigns to encourage mental health care has grown in popularity.
c. The public has become more accepting of mental health treatments.

Antidepressant use among people aged 12 and increased by 400 % in the United States, according to the data of Centers for Disease Control and Prevention (CDC). Increased antidepressant use has been a gradually prevalent trend in most industrialised countries, according to data acquired from public health authorities in Canada, Western Europe, and Australasia. Mental health experts have observed an overall 20 % rise in anti-depressant intake among people since the

second COVID-19 wave devastated the country. Data shows that the sale of antidepressants in April 2019 amounted to about Rs 189.3 crores. In June, it dropped to Rs 172.1 crores and increased further in July 2020 with Rs 196.9 crores. October 2020, it further rose to Rs 210.7 crores and reached its peak in April 2021 at a record of rupees 217.9 crores [5].

❖ BENEFITS OF HERBAL DRUGS OVER ALLOPATHIC DRUGS

Although allopathic drugs have long been the most widely accepted medicine, people are increasingly turning to herbal therapy. This is related to the following allopathic medication drawbacks:

i. Its relief from ailments is only symptomatic,
ii. It has serious and frustrating side effects,
iii. It is very costly.

Because of the following characteristics, herbal medicine are preferred these types of circumstances,

a. Less expensive and more reasonable,
b. Directly corresponds to the patient's beliefs,
c. More accessible,
d. Time tested,
e. Considered natural and safe,
f. Considered to have less or no side effects.

❖ HERBAL DRUGS FOR DEPRESSION AND ANXIETY

Herbal drug used as antidepressant because they have no side effect and considered as natural and safer.Depression is the common mental illness with severe consequences to human fitness. Many people are gradually turning towards herbal medicine in order to find out the multi-target antidepressants with a low level of toxicity.

1. *Areca catechu*

Areca catechu Linn., is a slim monoecious palm belonging to the Arecaceae family. This plant, native to South East Asia, has been used since time immemorial time for its psychotropic and therapeutic properties. Areca fruits and seeds contain various biochemical substances including polyphenols, fats, vitamins and parasympathomimetic alkaloids. Areca consumption can produce psychostimulant effect(such as euphoria) which leads to increase the capacity to work [6].
Various studies included behavioural (acute and sub-chronic forced swim tests) and biochemical (monoamines and their metabolite levels using high performance liquid chromatography) are done to look into the potential antidepressant efficacy of *Areca catechu* nut ethanol extract and its various fractions.

Investigation done to observe the anti-depressant like activity of *Areca catechu* nut ethanolic extract (ACEE) using behavioural tests in rats. Forced swim test (FST) and tail suspension test (TST) were used to assess the anti-depressant like effect of ACEE rats. The*Areca catechu*nut ethanolic extract (ACEE) did not produce motor incoordination in rats.
Results suggest that the *Areca catechu* nut ethanolic extract 50mg/kg possess potential anti-depression like effect without generalized CNS depression [7].

2. *Albizia lebbeck*

The plant *Albizia lebbeck Linn*., is a large deciduous tree belonging to the family Mimosaceae. A study was designed to investigate the antidepressant effects of *Albizia lebbeck* leaves in various animal depression models. The alcoholic extract (70% v/v ethanol) of *Albizia lebbeck* leaves (200 and 400 mg/kg. p.o) was administered once daily for seven successive days to separate groups of young male swiss albino mice. The immobility periods of control and treated mice were recorded in two behavioural despair models forced swim test (FST), tail suspension test (TST) and the effect ofextract on locomotorfunction of mice was studied using actophotometer. The plant possesses CNS depressant activity [8, 9]. Acute toxicity was investigated up to a dosage of 1 g/kg (two times more than the active dose). We should point out that the extract showed no signs of toxicity even at this dosing level. As a result, *Albizia lebbeck* had an antidepressant-like effect in mice in both the FST and TST tests [10].

3. *Allium cepa*

Allium cepa (also known as onion) is a perennial herb with the stem in the underground bulb. Onions belong to the Liliaceae family, while some authors mention them as Alliaceae family. Common onion has one or two leafless flower stalks reaching 75–180 cm (2.5–6 feet) in height [11]. Few studies demonstrated that onion shows antidepressant effect. Samad et al. pointed out different studies which assessed the useful impact on the single immobilization of biochemical and behavioural improvements through *Allium cepa* powder. *Allium cepa* powder (200 mg/kg/day) was given to mice in a research group, dissolved in water when 14 days of drinking water were obtained in the control group. After 14 days of checking, *Allium cepa*treated mice were split into stressed classes again. Results show that *Allium cepa* could be useful for the treatment of anxiety, depression and memory control [12].

4. *Bacopa monniera*

The use of herbal products has increased tremendously in the western countries as well as in developed countries. One of the most important and valuable medicinal plants, widely used therapeutically in the orient and becoming increasingly popular is *Bacopa monniera*, a well known nootropic herb. *Bacopa monniera* widely known as Brahmi are considered as 'Medhya Rasayanas' in Ayurveda which means brain tonic. Brahmi is a spreading creeper, sweet in taste and highly valued classic brain and nervine tonic. It is used in the indigenous system of medicine for the treatment of various disorders of human being such as cardiac, respiratory and neuropsychopharmacological disorders like insomnia, insanity, depression, anxiety, psychosis, epilepsy, and amnesia or memory impairment [13].

To assess the antidepressant-like effect of MEBM forced swimming test (FST), tail suspension test (TST) and measurement of locomotor activity test (MLAT) have been done in mice.
Results showed that a strong and dose-dependent antidepressant effects in different mice models. The main findings of the MEBM significantly reduced the duration of immobility times in the forced swimming test ($p < 0.001$).
Results clearly demonstrate that the methanolic extract of *Bacopa monniera* possesses antidepressant-like activity in the animal behavioural models [14].

5. *Clitoria ternatea*

Clitoria ternatea is well known tropical perennial climber herb from family Fabaceae with slender downy stem, found throughout the tropical region of India, growing wild and also in gardens, bearing white or blue flowers. It is commonly known as “Aparajita” in Bengali, “Koyal” in Hindi and “Butterfly pea” in English. The extracts of *Clitoria ternatea* have been used as an ingredient in “Medhya Rasayanas” as a rejuvenating herbal formulation for treatment of various neurological disorders and to strengthen intellectual ability. The root part of *Clitoria ternatea* has been used for its laxative, purgative, diuretic, inflammation, indigestion, constipation, fever, arthritis, eye ailments, sore throat and anthelmintic [15].
The methanolic extract of *Clitoria ternatea* at the doses of 100 - 400 mg/kg, p.o has shown antidepressant effect in tail suspension test in mice. The extract of *Clitoria ternatea* significantly decreased the duration of immobility at the doses of 100 - 400 mg/kg. The decrease in the duration of immobility was more at dose of 400 mg/ kg of *Clitoria ternatea* as compared to fluoxetine, 10 mg/kg [16].

6. *Curcuma longa*

Major depressive disorder (MDD) is the most common psychiatric disorder. In 2017, the World Health Organization announced that indeed depression was the leading cause of disability and ill health worldwide, with more than 300 million people living with depression [17]. Although the antidepressant mechanisms of *Curcuma longa* (curcumin) on mental disorders are not yet entirely elucidated, there has been more and more research focusing on related studies in recent years. As one of the most rapidly growing fields in the psychiatric research, different mechanisms for the antidepressant effects of *Curcuma longa* (curcumin) have been proposed, as shown in Figure 1. In the past decades, growing evidence has supported that *Curcuma longa* (curcumin) could be in favour of enhancing the antidepressant efficacy via multiple mechanisms of action [18].

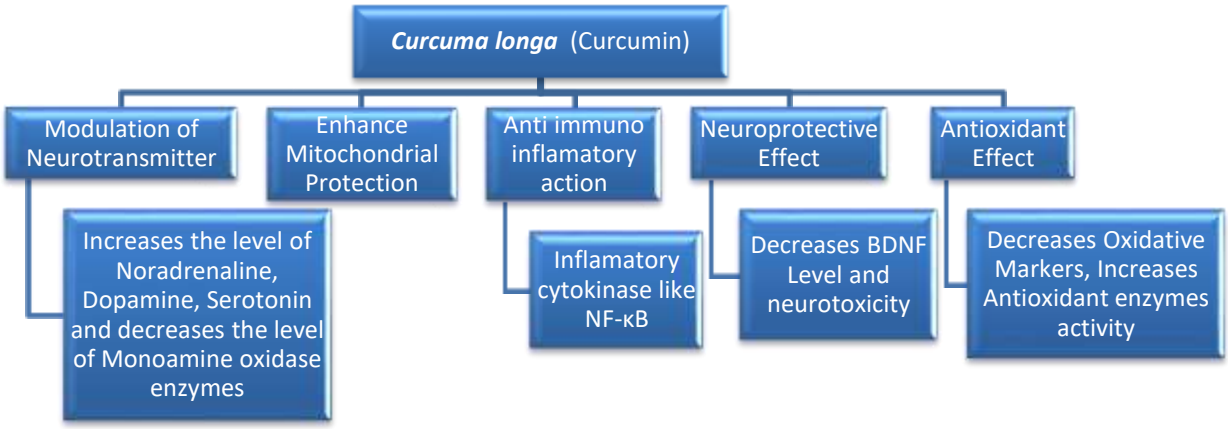

Figure 1 shows Potential Antidepressant Mechanisms of Curcumin

Depression is a severe, chronic, and recurring mental health disorder, which prevalence and mortality rate have increased in recent years. Several theories are proposed to elucidate the mechanisms of depression, such as the involvement of inflammation and the release of cytokines. Alternative treatments have been developed to improve outcomes of the commonly used drugs, and the use of *Curcuma longa* stands out. Its primary compound is curcumin that exhibits

antioxidant and anti-inflammatory effects. It is also effective in improvement in depression and anxiety behaviour in humans. It can increase monoamines and brain-derived neurotrophic factor levels and may inhibit the production of pro-inflammatory cytokines and neuronal apoptosis in the brain [19].

7. *Cimicifuga racemosa*

Cimicifuga racemosa Linn., a well-known medicinal plant widely distributed in China, is a species of *Cimicifuga* genus. It is recorded in the Compendium of Materia Medica that *Cimicifuga racemosa Linn*. is used for improving the symptoms of depression, anxiety, night sweating and hot flushes etc. The alcoholic extract of *Cimicifuga racemosa Linn*. (Brand name: XIMINGTING, State Drug Approval Number: Z20050748) was approved for the treatment of perimenopausal symptoms by China State Food and Drug Administration in 2005, whose main active constituents are believed to be *Triterpenoid saponins* (Li et al., 2002). In the clinical trials in China, XIMINGTING (XMT) displayed antidepressant-like effects when used to treat the women with perimenopausal symptoms (unpublished data). However, no research has been reported on the antidepressant-like effects and the pharmacological mechanisms of XMT in rodents [20]. *Cimicifuga racemosa* (CR) extract Ze 450 was studied in 442 unselected ambulatory female outpatients with menopausal complaints under daily practice conditions. Treatment with CR in unselected patients with climacteric complaints under the conditions of daily practice resulted in a significant improvement of menopausal symptoms assessed by the total KMI score and its sub-item scores with an effect size similar to that in aprevious randomized, controlled clinical trial [21].

8. *Crocus sativus*

Crocus sativus Linn., belonging to Iridaceae family, is commonly known as saffron. It is a perennial herb widely cultivated in Iran and other countries, such as India and Greece. Commercial saffron is a spice comprises of dried red stigma with a small portion of the yellowish style attached to the flower of *Crocus sativus.* From decades saffron was used in traditional Chinese medicines for its expectorant, aphrodisiac, and antispasmodic effects. *Crocus sativus* was found to be effective as similar to fluoxetine in the treatment of mild-to-moderate depression. In study by Melnyk et al. (2010), kaempferol (the active constituent in saffron petals) at doses of 100 and 200 mg/kg in mice and 50 mg/kg in rat reduces depressive symptoms similar to fluoxetine [22]. According to the study conducted by Murray and Lopez, depressive disorder is one of the most prevalent psychiatric diseases and has been estimated to affect up to 21% of the world's population. Majority of patients are often reluctant to take synthetic antidepressant drugs in their appropriate doses because of the anticipated side effects such as the inability to drive a car, dry mouth, constipation, and libido. Hence, plant extracts are some of the most attractive sources of new drugs and have been shown to produce a better result with low side effects in the treatment of depression [23]. In the placebo-comparison trials, saffron had large treatment effects and when compared with antidepressant medications, it had similar antidepressant efficacy. Saffron's antidepressant effects potentially are due to its serotonergic, antioxidant, anti-inflammatory, neuro-endocrine and neuroprotective effects [24].

9. *Emblica officinalis* (Amla)

In the traditional systems of medicine, many plants and formulations have been used to treat depression for thousands of years. *Emblica officinalis* (EO) contains tannic acid as its main ingredient and this compound has been shown to have non-selective mono-amine oxidase activity. Phytochemical analysis of the dried powder of *Emblica officinalis* contains tannins, alkaloids, carbohydrates, polyphenols and amino acids. This drug was administered to the animals 60 minutes prior to the behavioural evalution in acute study. For chronic study, a new set animal were used. They were grouped as in acute study and were administered this drugs for a period of 10 days. Behavioural evaluation was carried out 60 minutes post drugadministration on 10th day [25]. Antidepressant-like activity of *Emblica officinalis* fruits (Family: Euphorbiaceae) was evaluated in Swiss young male albino mice employing tail suspension test and forced swim test. Aqueous extract (200 and 400 mg/kg) of the fruits was administered orally for 14 successive days to mice. On day 14, 60 min after extract administration, animals were subjected to tail suspension test and forced swim test.

The extract significantly decreased immobility period in both tail suspension test and forced swim test, indicating significant antidepressant-like activity. The lower dose (200 mg/kg) of the extract showed better antidepressant-like action.

The aqueous extract might produce antidepressant-like effect by interaction with α(1)-adrenoceptors, dopamine D(2)-receptors, serotonergic and GABA(B) receptors. In this study, aqueous extract was found to contain 2.94 % of ascorbic acid. So, ascorbic acid and other constituents like flavanoids, tannoid principles, and polyphenolic substances present in the aqueous extract of *Emblica officinalis* might be responsible for its antidepressant-like activity. Thus, aqueous extract of *Emblica officinalis* showed antidepressant-like activity probably by inhibiting MAO and GABA; and also due to its antioxidant activity [26].

10. *Zingiber officinale* (Ginger)

Ginger (*Zingiber officinale* Roscoe), a well-known spice plant, has been used traditionally in the treatment of a wide variety of ailments. The main objective of the work is to evaluate the antidepressant and anti-nociceptive activity of ethanolic extract of *Zingiber officinale* in Swiss albino mice [27].

The antidepressant property of *Zingiber officinale* as well as its interaction with conventional antidepressant drug using forced swim test and to evaluate possible mechanism involved in its action. Anti-nociceptive activity was evaluated by acetic acid induced writhing and its interaction with conventional analgesic drug was also noted. The rhizomes of ginger were authenticated and extraction of dried rhizomes was done by using soxhlet apparatus to obtain its ethanolic extract.The alcoholic extract of *Zingiber officinale* (300mg/kg, p.o and 150mg/kg, p.o) for antidepressant activity significantly reduced the immobility time in mice ($P<0.05$) as compared to the vehicle control. The extract of *Zingiber officinale* (100 and 200 mg/kg, p.o.) significantly suppressed the acetic acid-induced writhing response in a dose-dependent manner in mice ($P<0.05$) as compared to the vehicle control. The plant extract of *Zingiber officinale* showed significant antidepressant activity in forced swim test model and significant anti-nociceptive effect in acetic acid induced writhing [28].

Plant Name	Part used	Extract used	Results	References
Areca catechu	Palm, Fruit	Dichloromethane, Ethanolic	Decreases the duration of immobility time (sec) in FST and TST tests.	[29]
Albizia lebbeck	Bark	Ethanolic	Shows antidepressant effect in mice in both the FST and TST tests.	[30]
Allium cepa	Bark	Ethanolic	Onion exerted antidepressant activity in a behavioural model that acted independently of the hypothalamic pituitary adrenal axis.	[31]
Asparagus racemosus	Root	Methanolic	Found one or two measures of memory to have a statistically significance difference.	[32]
Bacopa monniera	Aerial part	Methanolic	Methanolic extract of *Bacopa monniera* possesses antidepressant-like activity in the animal behavioural models.	[33]
Clitoria ternatea	Plant powder	Methanolic	*Clitoria ternatea* may be served as a potential resource for natural psychotherapeutic agent against depression	[34]
Curcuma longa	Root (rhizome)	Mehanolic	It increase monoamines and brain derived neurotrophic factor level may inhibit the production of pro-inflammatory cytokines and neuronal apoptosis in the brain.	[35]
Cimicifuga racemosa	Root	Ethanolic	Improvement of menopausal symptoms assessed by the total KIM score and its sub-item scores with an effect size.	[36]
Crocus sativus	Petals	Aqueous and ethanolic	It isfound to be effective as similar to fluoxetine in the treatment of mild-to-moderate depression.	[37]
Emblica officinalis	Fruit	Aqueous	It decreases the duration of immobility.	[38]
Glycyrrhiza uralensis	Root	Aqueous	It produces the anti-depressive effect on chronic unpredictable stress of depression model rats and its mechanism may be associated with its neurogenesis protective effect.	[39]
Glycyrrhiza glabra	Root	Aqueous	Increase of brain norepinephrine and dopamine, but not by increase of serotonin. Monoamine oxidase inhibiting effect of liquorice may be contributing favourably to the antidepressant-like activity	[40]
Hypericum perforatum	Aerial part	Aqeous, ethanolic	Decreased the immobility times of mice in the FST and TST	[41]
Momordica charantia	Seed, root	Methanolic	Significantly decreasing the immobility time in Tail Suspension test	[42]

Nardostachys jatamansi	Root, Rhizome	Methanolic	Statistically significant result with increasing dose and had synergic effect when given along with fluoxetine.	[43]
Tinospora cordifolia	Whole plant	Aqueous	Increasing the levels of monoamines like noradrenalin, serotonin, and dopamine, and decreasing the levels of GABA.	[44]
Zingiber officinale	Rhizome	Hydro-alcoholic	Showed antidepressant activity in FST test model and significant anti-nociceptive effect acetic acid.	[45]

Table 1 Shows Antidepressant Effect of Plants

❖ CONCLUSIONS

Day by day more and more individuals are suffering from various psychological diseases, particularly sadness, anxiety, and sleeplessness. These mental diseases have a significant financial impact on society in addition to having an impact on people's everyday lives. Growing research has been done in recent years on the psychopharmacology of plants. Large amounts of evidence suggest that many complex psychotropic effects of herbs may aid in the treatment of depression, anxiety, and sleep disturbances.

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