Role of herbal drugs on neurotransmitters for treating various CNS disorders: A review

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Neurotransmitters are chemical messengers in the human body and are associated with several CNS disorders. Plant drugs can be used as agonist/antagonist/modulator to neurotransmitters to treat CNS disorders like Alzheimer’s disease, Parkinson’s disease etc. The current review comprises the role of various neurotransmitters in CNS diseases and plants to treat them. This review compiles most of the scientific research related to the role of neurotransmitters and potential plants to treat various CNS disorders. Authors hope that researchers will utilize this current knowledge to explore and establish the potential herbal drugs to treat CNS disorders. This review has been compiled using references from major databases such as Chemical Abstracts, Medicinal and Aromatic Plants Abstracts, ScienceDirect, SciFinder, Google Scholar, Scopus, PubMed, Springer Link, and books, without limiting the dates of publication. General web searches were also carried out using Google and Yahoo search engines by applying some related search terms (e.g., Neurotransmitters, herbal drugs, pathophysiology and CNS disorders). The articles related to agriculture, ecology, and synthetic works and those using languages other than English or Persian have been excluded. Neurotransmitters play an important role in the pathophysiology of various CNS disorders. Plants can be used as potential drugs to treat various CNS disorders as confirmed by various pharmacological studies illustrated in this review. This review discusses the current knowledge of neurotransmitters, their role in CNS disorders and herbal drugs that can be used to treat these diseases.

Keywords: Plant drugs, Phytotherapy, Phytoconstituents, Bioactive, Acetylcholine, GABA, Glutamate, Serotonin, Catecholamines

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Neurotransmitters are chemicals that travel across the synapse and allow communication between neurons throughout our brain and body¹.

The general properties of neurotransmitters are as follows:
1. They are synthesized in the presynaptic neuron and localized to vesicles in the presynaptic neuron.
2. They are released from the presynaptic neuron under physiological conditions and rapidly removed from the synaptic cleft by uptake or degradation.
3. They bind to the receptor present on the postsynaptic neuron to elicit a biological response.

There are two types of neurotransmitters: inhibitory and excitatory². Excitatory neurotransmitters are exciting the brain and also, they are what stimulate the brain. Those that calm the brain and help create balance are called inhibitory. Inhibitory neurotransmitters balance mood and get easily depleted when the excitatory neurotransmitters are overactive.

Inhibitory neurotransmitters
1. Serotonin is an inhibitory neurotransmitter³. Adequate amounts of serotonin are necessary for a stable mood and to balance any excessive excitatory (stimulation) neurotransmitter in the brain⁴. Serotonin also regulates many other processes such as carbohydrate cravings, sleep cycle, pain control, and appropriate digestion⁵. Decreased serotonin levels also affect functioning of body’s immune system.
2. GABA is another inhibitory neurotransmitter when GABA is out of range (high or low levels) it is likely that an excitatory neurotransmitter is firing too often in the brain⁶. GABA will be sent out to attempt to balance this stimulating firing.
**Excitatory neurotransmitters**

1. Acetylcholine is very widely distributed excitatory neurotransmitter that triggers muscle contraction and stimulates the excretion of a certain hormone. In the CNS, it is involved in wakefulness, attentiveness, learning and memory, anger, aggression, sexuality and thirst among other things.

2. Dopamine is an excitatory neurotransmitter involved in controlling movement and posture. It also modulates mood and plays a central role in positive reinforcement and dependency. When dopamine is either elevated or low, we can have issues such as not remembering where to put our keys, forgetting what a paragraph said when we just finished reading it or simply daydreaming and not being able to stay on task.

3. Norepinephrine helps to make epinephrine. This neurotransmitter can cause anxiety as well as some mood dampening effects at elevated excretion levels, low levels of neurotransmitter cause low energy, decreased focus and sleep cycle problems.

4. Epinephrine is an excitatory neurotransmitter. This neurotransmitter will often be elevated when ADHD-like symptoms are present. Long-term stress or insomnia can cause epinephrine levels to be depleted. Epinephrine also regulates heart rate and blood pressure.

Apart from above, neurotransmitters can also be classified by their chemical nature as per their basic ring and arrangement of the side chain present (Fig. 1).

The brain uses neurotransmitters to tell the heart to beat, lungs to breathe, stomach to digest. They can also affect mood, sleep, concentration, weight and can cause adverse symptoms or any other pathological condition when they are out of balance.

The main function of neurotransmitters is to relay the information from one nerve cell to another nerve cell to produce a quick response toward any external or internal stimuli (Fig. 2).

In contrast to CNS disorders, neurotransmitters have a positive pathophysiological role in the development of diseases including dementia, anxiety, neurodegenerative disorders, epilepsy, stroke as well as Parkinson’s disease, Alzheimer’s disease and Huntington’s disease and mood disorders. Various studies involving different kind of neurotransmitters revealed that herbal drugs can affect the normal physiology pertained by a particular neurotransmitter because of their agonistic, antagonistic or modulator activity and hence can be used in the treatment of several CNS disorders because the currently available synthetic drugs show a profound adverse reaction due to which the treatment strategies for various CNS disorders is limited.

Current review covers the role of different neurotransmitters in various CNS disorders and the plants acting on those neurotransmitters to treat CNS disorders.

![Fig. 1 — Chemical nature of neurotransmitters](image1)

![Fig. 2 — Schematic representation of neurotransmission across the neurons](image2)
Role of neurotransmitters

**Acetylcholine**

All the muscarinic receptors (M₁-M₅) are located in different parts of the brain and hence are very widely involved in various neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease. In the case of Alzheimer’s disease M₁ and M₂ receptor agonists have been proved to be an effective medication in the management of this disease. Muscarinic receptors are also involved in schizophrenia, especially M₅ and M₄ receptors. Agonists of these receptors have been found to be effective in the treatment of schizophrenia. M₄ antagonists have been found to be effective as antiparkinsonian agent revealed by several animal studies. Except for memantine, all other FDA approved the medication for symptomatic treatment of Alzheimer’s disease are acetylcholine esterase inhibitors but the efficacy is limited to first two years of treatment, and also they possess several adverse effects that limit their action as an effective drug for the treatment of Alzheimer’s disease.

The postulated mechanism by which acetylcholine is involved in CNS disorders may be understood by (Flow diagram A).

**Gamma-Aminobutyric Acid (GABA)**

GABA is the neurotransmitter associated with depressive disorders, and several studies revealed that there is a significant decrease in the GABA levels in various types of depressive disorders including panic disorders and unipolar disorders (Flow diagram B). Premenstrual dysphoric disorder (PMDD) has also been found to be associated with the reduced GABA levels during the follicular phase. Several pieces of evidence have been found showing that many antidepressant drugs increase the level of GABA in the cortical region as well as some specific agents that target GABA receptors play an important role in the treatment of several depressive disorders.

**Glutamate**

Glutamate is an excitatory neurotransmitter and if the glutaminergic system becomes overactive can lead to Parkinson’s disease as demonstrated in several studies (Flow diagram C).

Glutamate receptors can be divided into two groups according to the mechanism by which their activation gives rise to a postsynaptic current. Ionotropic glutamate receptors form the ion channel pore that activates when glutamate binds to the receptor.
Ionotropic receptors tend to be quicker in relaying information. Metabotropic glutamate receptors indirectly activate ion channels on the plasma membrane through a signaling cascade that involves G proteins. Metabotropic receptors are associated with a more prolonged stimulus. Several antagonists of NMDA have been used for symptomatic treatment of Parkinson’s disease. Other than this glutaminergic system is also involved in the development of several disorders like schizophrenia, epilepsy, anxiety, Alzheimer’s disease, dementia, depression, tolerance, sensitization. Another study also revealed that the NMDA blockers also play an important role as mood stabilizers and used as antidepressants.

**Serotonin**

Serotonin is a monoaminergic neurotransmitter which is involved in the pathophysiology of several mental disorders, especially schizophrenia. One study shows that different antagonists of serotonin can cause mental disorders in laboratory animals suggesting that this may be due to decreased levels of serotonin. Several serotonergic receptors have been found to be involved in depression and other mental disorders, but only 5-HT1A is clinically evaluated (Flow diagram D).

Besides this, other receptors like 5-HT1B, 5-HT3 and 5-HT6 are also involved in depressive conditions but lack clinical evidence. 5-HT7 receptor antagonists have shown improvements in depressive states. 5-HT1A is more extensively found to be involved in various psychiatric disorders like depression, anxiety and schizophrenia and hence can be an important target for treatment of these diseases.

**Catecholamines**

The complete review of the catecholamines is out of scope of this article, however, we have highlighted some keypoints which are important to understand the effects of herbal drugs targeting these neurotransmitters. Catecholamines include adrenaline, noradrenaline, and dopamine. Adrenaline and noradrenaline act through adrenoreceptors, i.e., α-Adrenoceptors and β-adrenoceptors. Evidence show that antidepressant drugs increase the level of α1-Adrenoceptors and blockade of these receptors may lead to depressive conditions. Antagonists of α2-Adrenoceptor also possess antidepressant activity. It is also suggested that β-adrenoceptor agonists can also act like antidepressants. Dopamine acts through dopaminergic receptors and several agonists of D2/D3 receptors show antidepressant activity.

Table 1 summarizes the involvement of different neurotransmitters in various CNS disorders.

### Plants active on neurotransmitters

#### Acetylcholine

**Amanita muscaria** (L.) Lam.

It is a fungus that belongs to the family *Amanitaceae*. It is native to Siberia and North America commonly known as *Amanita*, fly agaric. It is cholinergic receptor agonist more potent than acetylcholine. Main chemical constituent responsible for its cholinergic effect is muscarine. Muscarine salt has all the activity similar to acetylcholine as it causes contraction of the horse ureter and carotid artery chain in vitro and slows down the isolated auricles of the guinea-pig and rabbit, and the frog heart. It also causes a reduction in blood pressure, although in vitro it produces either constriction or dilatation of the blood vessels of the rabbit ear.

**Pilocarpus jaborandi** Holmes

It bears the common name Indian hemp belonging to the family *Rutaceae*. It is commonly found in Tropical America and West Indies. Its major constituent pilocarpine is a potent agonist for muscarinic (postganglionic) receptor stimulation and nicotinic (ganglionic) receptor stimulation. Pilocarpine has also been used in the treatment of xerostomia or dry mouth and shown a better efficacy than placebo-controlled models.

**Areca catechu** L.

It is commonly known as betel nut, areca nut or supari (Hindi) and is a plant of family *Arecaceae*. Mainly seeds of this plant are used. Arecoline, the main chemical constituent stimulates both muscarinic and nicotinic receptors (in ANS and CNS). Several studies have been done to establish its activity like it causes contraction of guinea pig ileum, smooth...
Physostigma venenosum Balf.
The common names for this plant are Calabar, ordeal, or esere bean. It belongs to the family Fabaceae (pea or bean family). Its main constituent physostigmine, Inhibits acetylcholinesterase in postganglionic nerves & myoneural nerve endings (somatic motor neurons)\textsuperscript{20}. It increases the acetylcholine level peripherally as well as centrally in a dose-dependent manner\textsuperscript{20}. Physostigmine is more potent than other cholinesterase inhibitor drugs in the treatment of memory loss in aging primate models\textsuperscript{20}.

Atropa belladonna L.
It is commonly known as belladonna herb belonging to the family Solanaceae. Leaves are rich in its principle active constituent atropine. Atropine is a competitive antagonist for the muscarinic acetylcholine receptor types M1, M2, M3, M4 and M5\textsuperscript{21}. With atropine molecular acetylcholine/receptor reaction is modified and conductance is also lowered\textsuperscript{22}.

Hyoscyamus niger L.
It is commonly known as henbane and belongs to the family Solanaceae. The main chemical constituent hyoscyamine has two forms, i.e., (+) –hyoscyamine and (-) hyoscyamine. (+) hyoscyamine is non-competitive whereas (-) hyoscyamine is a competitive antagonist of acetylcholine\textsuperscript{23,24}. Hyoscyamine is used as sedative in premedication in anesthesia and possesses other several effects which are likely to be involved in the treatment of various CNS disorders\textsuperscript{24}.

Gamma-Aminobutyric Acid (GABA)

<table>
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Table 1 — Involvement of different neurotransmitters in various CNS disorders

### Neurotransmitters

- **Acetylcholine**: A very widely distributed excitatory neurotransmitter that triggers muscle contraction and stimulates the excretion of certain hormones. It is involved in wakefulness, attentiveness, anger, aggression, sexuality, and thirst, among other things.
- **Dopamine**: A neurotransmitter involved in controlling movement and posture. It also modulates mood and plays a central role in positive reinforcement and dependency.
- **GABA (gamma-aminobutyric acid)**: An inhibitory neurotransmitter that is very widely distributed in the neurons of the cortex. GABA contributes to motor control, vision, and many other cortical functions. It also regulates anxiety.
- **Glutamate**: A major excitatory neurotransmitter that is associated with learning and memory.
- **Norepinephrine**: Important for attentiveness, emotions, sleeping, dreaming, and learning. Norepinephrine is also released as a hormone into the blood, where it causes blood vessels to contract and heart rate to increase.
- **Serotonin**: Regulating body temperature, sleep, mood, appetite, and pain.

### Associated diseases

- Alzheimer’s disease is associated with a lack of acetylcholine in certain region of brain.
- The loss of dopamine in certain parts of the brain causes the muscle rigidity typical Parkinson disease.
- Some drugs that increase the level of GABA in the brain are used to treat epilepsy and to calm the trembling of people suffering from Huntington’s disease.
- Alzheimer disease whose first symptoms including memory malfunctions. Norepinephrine plays a role in mood disorders such as manic depression.
- Depression, suicide, impulsive behavior, and aggressiveness all appear to involve certain imbalances in serotonin.
times less than picrotoxinin. Other than GABA\textsubscript{A} picrotoxinin also antagonizes GABA\textsubscript{C}, glycine (moderate), and 5HT3 (weak) receptors. Both picrotoxinine and picrotin are equally potent in blocking the glycine receptor\textsuperscript{25}.

**Ginkgo biloba L.**

It is a Chinese plant commonly known as maidenhair tree. It belongs to the family Ginkgoaceae. It mainly contains a sesquiterpenoid lactone, i.e., bilobalide which has the structural similarity to picrotoxinin and thus it is also an antagonist of GABA\textsubscript{A} and GABA\textsubscript{C} receptors. Although bilobalide is structurally similar to Picrotoxinin, it shows a huge difference in vivo. Picrotoxinin is a convulsant while bilobalide is an anticonvulsant\textsuperscript{25}.

**Amanita muscaria** (L.) Lam.

It is commonly known as fly agaric or fly amanita belonging to the family Amanitaceae. These mushroom are mainly found in France, and Romania and its major component is muscarine. It is an agonist of GABA receptors and widely used to study the ionotropic GABA receptors. It is a more potent agonist of GABA\textsubscript{C} than GABA\textsubscript{A} receptor\textsuperscript{25}.

**Lavandula angustifolia** Mill.

Its synonyms are Lavender; Khas (Hindi) & it belongs to Family Lamiaceae. It has long traditional use in the therapy of depressive disorder, contains linalool and linalyl acetate. Mainly the leaves and flower part are used.

Lavender oil is used as herbal medicine, gives relaxation while giving massage therapy. It modulates GABAergic neurotransmission on GABA\textsubscript{A} receptor that non-selectively reduces the influx of calcium, enhances inhibitory tone and reduces depression.

The herbal extract of lavender with imipramine has a synergistic effect that plays more effective role in depression. People also use it in toothaches, joint pains, to repel mosquitoes and other insects, flavoring agent, etc.\textsuperscript{25}

Anxiolytic, depression & similar to this activity was explained by performing behavioral tests like marble buying test, elevated plus maze, locomotor activity, serotonin syndrome on adult male swiss albino mice (30-45 g)\textsuperscript{28,29}.

**Melissa officinalis** L.

Its synonyms are Lemon balm, Balm mint & it belongs to Family Lamiaceae. It is a calming herbaceous plant from mint family having the gentle fragrance of lemon. It contains citronellal, linalyl acetate, caryophyllene, geraniol, rosmarinic acid and eugenol. Essential oil is used in aromatherapy, contains eugenol that calms muscles.

Extract of lemon balm contains rosmarinic acid, inhibits GABA transaminase, enhances GABAergic activity in the brain and provides calming effect on depression and also in anxiety. It also has a carminative, diaphoretic and hypotensive effect.

The anxiolytic & antidepressant-like effect was discussed by performing some behavioral test on male & female wistar rat in elevated plus-maze (EPM), forced swimming (FS) and open field (OF) tests after oral route administration of leaf extract of *Melissa officinalis*\textsuperscript{30}.

**Rosa centifolia** L.

Its synonyms are Rose petals, Gulkand (Hindi), Shatapatri. It belongs to Family Rosaceae. It is a beautifully fragrant flower plant, containing volatile oil, pectin, tannic acid, flavonoids, nicotinamide, fruit acids, salts and coloring matter. Rose hips, flower, and leaves are mainly used. It has a neuropharmacological effect. The *Rosa centifolia* contains flavonoid that possesses an effective anti-depressant and anxiolytic activity in numerous studies. It modulates GABAergic neurotransmission, enhances the inhibitory tone of the nervous system, improves the symptoms like restlessness, disturbed sleep and calms depression and anxiety. It has other uses also such as hepatoprotective, reproductive tonic, anti-inflammatory activity, and diaphoretic, as well as a carminative. The anxiolytic-like effect was observed by using geller conflict Vogel anxiety model on mice by i.p route\textsuperscript{29}.

**Piper methysticum G. Forst.**

Synonyms are Kava, Ava pepper and Family is Piperaceae. *Kava* is a traditional south pacific medicinal plant used for treating anxiety. It is the most effective natural remedy for anxiety. Root is used mainly. It contains kavain, dihydrokavain, methysticin and yangonin which potentiates GABA\textsubscript{A} receptor activity. Kavain and methysticin are able to inhibit voltage-gated sodium channels and voltage-gated calcium channels\textsuperscript{29}.

It has been reported that the consumption of alcohol is avoided while taking of *Kava* because it interacts poorly. It may be effective alternatives to the drugs like benzodiazepines and tricyclic anti-depressants for the treatment of anxiety.
Passiflora edulis Sims.
Its synonyms are Passion flower, Maypop, Apricot vine, Jhumkalata (Hindi) and the Family is Passifloraceae. It is an American traditional medicine that has been used to overcome wakefulness and restlessness. It contains flavonoids, indole alkaloids like harmane, harmine, and harmol.
Passiflora incarnata modulates GABAAergic system including affinity to the GABA A and GABA B receptors and also effects on GABA uptake that suppresses anxiety and gives relaxation to CNS.

Valeriana officinalis L.
Its synonyms are valerian, Garden valerian, tagar (Hindi/Sanskrit) belonging to the Family Valerianaceae. The roots of valerian are used for medicinal purposes. It contains volatile oil, flavanones, and alkaloids. The work of valerian is more effective than benzodiazepines. The constituents of valerian have an affinity to GABA A receptor and suppress the symptoms of anxiety. In place of hypnotic drugs, valerian is used as an alternative medicine for insomnia without producing side effects. 

Withania somnifera (L.) Dunal
Its synonyms are Ashwagandha, Indian ginseng, Poison gooseberry, Winter cherry and the Family is Solanaceae. It is a medicine that was classified in Ayurveda as 'Rasayana' that improves mental as well as physical performance. Ashwagandha contains withanolides which can interfere with the GABA neurotransmission and decreases neuronal activity that stabilizes the mood in patients.
It helps to induce sleep, uplift mood, and has calming effect on the brain, antioxidant property, anti-inflammatory property, etc.

Glutamate
Tabernanthe iboga Baill.
It is a plant of family Apocynaceae commonly known as iboga. This plant has the origin in Western Central Africa. It mainly contains ibogaine which is an indole alkaloid. Ibogaine is mainly a non-competitive antagonist of NMDA receptor. A concentration-dependent block of NMDA-induced currents (ICs, 3.1 PM at -60 mV) was caused slowly by ibogaine as demonstrated in whole-cell recordings from cultured rat hippocampal neurons.

Camellia sinensis (L.) Kuntze
It is commonly known as green tea and is a native of China and India. It belongs to the family Theaceae. The main chemical constituent theanine is an antagonist of NMDA receptor. Theanine prevents the death of cultured rat cortical neurons induced by glutamic acid. Although the binding capacity in all cases is markedly less than that of glutamic acid, theanine has a higher affinity for the AMPA/kainate receptors than for NMDA receptors.

Catecholamines
Hypericum perforatum L.
It bears the synonyms St John's wort (SJW), Choli Phulya (Hindi) & belongs to Family Hypericaceae. It is a flowering herbaceous plant, contains hyperforin and hypercin having highly effective role in the treatment of depression. Flowers, leaves, herb tops are used. It also contains flavonoids, tannins, volatile oils, etc.
The mechanism of the anti-depressant action by SJW is that it inhibits the nonselective re-uptake of neurochemicals (Dopamine, Norepinephrine, serotonin, GABA, and Glutamate) that decreases neurochemical degradation, enhances binding to many receptors and suppresses depression and condition along with it such as sleepiness, anxiety, etc.
SJW is also used in anxiolytic, heart palpitations, and symptoms of menopause. Anxiolytic activity of Hypericum was explained by performing open field test experiment on adult Charles Foster rats (180-200 g).

Crocus sativus L.
Its synonyms are Saffron, Saffron crocus, Crocus, Kesar (Hindi), Kumkuma (Sanskrit) belonging to Family Iridaceae. It is a Persian traditional medicinal flowering herbaceous plant used for its anti-depressant activity, belongs to the iris family with a pleasant odor. Mainly its dried stigma and style tops are used. It contains crocin, crocetin, safranal, picrocrocin and flavonoids among which safranal is the main constituent.
It is proposed that the constituent crocin inhibits the uptake of neurochemicals (Norepinephrine and Dopamine) that helps in improving mood and are effective in treating mild to moderate depression. It has also been proposed for increased serotonin level in the brain, the exact mechanism of action for this is unknown, but more specifically serotonin re-uptake in synapses might be inhibited by crocin. By this serotonin is stored in the brain longer.
It is also used as a flavoring agent, spice, fragrance in perfume, dye for cloth, menstrual cramps, etc.
**Rosmarinus officinalis L.**

Synonyms of this plant are Rosemary, Anthos, Rusmari (Sanskrit) belonging to the Family Lamiaceae. It is an Indian traditional medicinal plant belonging to mint family and has a pleasant aroma. It contains rosmarinic acid, camphor, caffeic acid, antioxidants, ursolic acid\(^{39}\). Its essential oil, extracts and herbal tea is used in the therapy of depressive disorders.

The ursolic acid inhibits the uptake of neurochemicals (dopamine, serotonin, and noradrenaline) and suppresses the condition of depression\(^{40}\).

**Drugs acting on multiple neurotransmitters**

**Crassocephalum bauchiense** (Hutch.) Milne-Redh

This plant belongs to the Family Compositeae. The leaf of the **Crassocephalum bauchiense** is used for medicinal purposes. It contains alkaloids. This plant acts by blocking dopamine D-2 receptors and active GABAergic systems\(^{31}\).

**Annona cherimola** Mill.

Its synonyms are ilama, ilama zapote, zapote de vieja, papausa, papauce or anona blanca, papause and it belongs to Family Annonaceae. The leaf of the **Annona cherimola** Mill. is used for medicinal purposes. This plant acts on GABAA/BZD; 5-HT1A receptors; increases DA and serotonin (5-HT) turnover\(^{31}\).

**Conclusion**

Neurotransmitters are very widely distributed in the human body and are involved in almost all activities. They are mainly concentrated in the brain and are also involved in the pathophysiology of various CNS disorders like AD and Parkinson’s disease which mainly include acetylcholine, dopamine, GABA, glutamate, catecholamines, and serotonin. It has also been proved that these neurotransmitters and their receptors can be regarded as an important molecular target for treating CNS disorders. The use of agonist/antagonist of these receptors can control CNS disorders to a great extent either symptomatically or at the molecular level by potentiating or blocking the activity of these neurotransmitters. Chemical constituents isolated from various plants have been the interesting tool of research for the researchers and are preferable over the synthetic drugs due to their minimal adverse events. This review describes how the plants have been established as the drug of choice for the treatment of various CNS disorders. This study also contains the various experimental studies and results in the field of medicinal plants research, and this will also open areas in the field of phytotherapy especially for medicinal plants used in long-term treatment of CNS disorders like AD, Parkinson’s disease, depression, and dementia.

Further study of such plants will help to breach the contemporary scientific studies with traditional and folklore claims and believes. Multitarget effects of plant bioactive are well established as in the case of **Crassocephalum bauchiense** and **Annona cherimola** Miller, and this review will help researchers to find out more such plants for the treatment of CNS diseases.

**Disclosure statement**

The authors report that there is no conflict of interest.

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