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# Treatment of anxiety and depression: medicinal plants in retrospect

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## ABSTRACT

Anxiety and depression are complex heterogeneous psychiatric disorders and leading causes of disability worldwide. This review summarizes reports on the fundamentals, prevalence, diagnosis, neurobiology, advancement in treatment of these diseases and preclinical assessment of botanicals. This review was conducted through bibliographic investigation of scientific journals, books, electronic sources, unpublished theses and electronic medium such as ScienceDirect and PubMed. A number of the first-line drugs (benzodiazepine, azapirone, antidepressant tricyclics, monoamine oxidase inhibitors, serotonin selective reuptake inhibitors, noradrenaline reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, etc.) for the treatment of these psychiatric disorders are products of serendipitous discoveries. Inspite of the numerous classes of drugs that are available for the treatment of anxiety and depression, full remission has remained elusive. The emerging clinical cases have shown increasing interests among health practitioners and patients in phytomedicine. The development of anxiolytic and antidepressant drugs of plant origin takes advantage of multidisciplinary approach including but not limited to ethnopharmacological survey (careful investigation of folkloric application of medicinal plant), phytochemical and pharmacological studies. The selection of a suitable plant for a pharmacological study is a basic and very important step. Relevant clues to achieving this step include traditional use, chemical composition, toxicity, randomized selection or a combination of several criteria. Medicinal plants have been and continue to be a rich source of biomolecule with therapeutic values for the treatment of anxiety and depression.

## INTRODUCTION

The development of anxiolytic and antidepressant drugs of plant origin involves ethnopharmacological survey (careful investigation of folkloric application of medicinal), phytochemical and pharmacological studies (*Figure 1*). The selection of a suitable plant for a pharmacological study is a very important step. Relevant clues to achieving this step include traditional use, chemical composition, toxicity, randomized selection or a combination of several criteria [1–3]. Selection of medicinal plants with a view to discovering new pharmaceutical agents based on its popular use is by far the most effective strategy [4]. The plants that have been used popularly for years constitute the most obvious source of botanical material for the investigation of therapeutically effective drugs. The collection of plant material, identification and deposition of specimen in the herbarium are generally followed by quantitative and qualitative analyses with different techniques including thin-layer chromatography, column chromatography, high-performance liquid chromatography, nuclear magnetic resonance, among other phytochemical techniques.

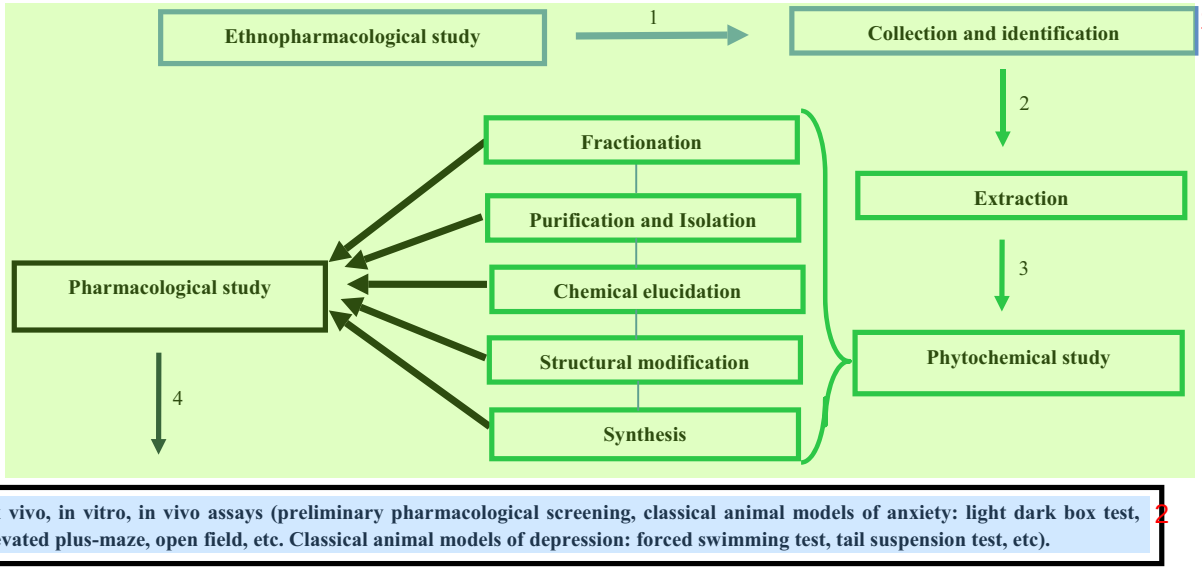


**Figure 1** Hypothetical model for the discovery of medicinal plant extracts and phytoconstituents with anxiolytic and/or antidepressant property (ies). (i) Selection of medicinal plant with anxiolytic and/or antidepressant potential based on local reports; (ii) Preparation of standard crude extracts; (iii) Phytochemical studies (sequential partitioning of crude extracts, purification and isolation of phytoconstituents, chemical elucidation or characterization of the isolates, structural modifications or synthesis of a new compound based on the chemical structure of isolates; (iv) Pharmacological study of anti-anxiety and antidepressant properties of standard crude extracts, fractions, isolated compounds or derivatives. Ex vivo, in vitro, in vivo assays (preliminary pharmacological screening, classical animal models of anxiety: light dark box test, elevated plus-maze, open field, etc. Classical animal models of depression: forced swimming test, tail suspension test, etc.).

Following the ethnopharmacological survey and phytochemical studies, biological investigations of botanicals are inevitable. Animal models of anxiety and depression have played relevant roles in the development of new drugs [5,6]. A well-validated test could lead to consistent preclinical and clinical findings of novel anxiolytic and antidepressant drugs. In recent times, some of the traditional preclinical approaches have witnessed modifications and innovations. This review sought to summarize background of anxiety and depression, pharmacological treatments, medicinal plants with anti-anxiety and antidepressant properties as well as preclinical strategies for the investigation of extract or phytoconstituents with potential anxiolytic and/or antidepressant activity (ies).

## Prevalence and diagnosis of anxiety and depression

Anxiety and depression are widely acclaimed as psychiatric disorders of global concern that are capable of compromising human welfare [7]. Anxiety disorder is characterized by cognitive, somatic, emotional and behavioural alterations [8]. About 4–6% of the global population suffer from various forms of anxiety disorders with such symptoms as high blood pressure, elevated heart rate, sweating, fatigue, unpleasant feeling, tension, irritability and restlessness [9,10]. These symptoms constitute negative impact to the patient, families and society. In the absence of treatment, patients would progress to depression and sometimes contemplate suicide [11]. Depression that was the fourth largest cause of disease's burden worldwide in 1990 is expected to be the second largest by 2020 [12]. The prevalence of major depressive disorder in community samples ranges from 5 to 9% for women and 2 to 3% for men [13]. Symptoms of depression include low, sad or depressed mood and/or loss of interests or pleasure in previously enjoyable activities [14].

## Neurobiology of anxiety and depression

An increase in the prevalence of these mental illnesses with mind-boggling questions in respect of its pathogenesis [15] has kept researchers groping in the dark for years. The comprehension of neurobiology of these diseases is important to effective treatment. The understanding of neural mechanism of drugs as well as the

prediction of possible response of patients to anxiolytic and antidepressant drugs could be greatly enhanced through the knowledge of the neurobiology [16].

The role of the limbic system in emotion was identified by James Papez in early 1930. He described the 'system of emotion' as one of the major pathways of the limbic systems that connect groups of brain structures (cingulate gyrus, hippocampus, hypothalamus and nuclei thalamus) around the brainstem [17]. Drevets [18] hypothesized anatomical circuits involving medial prefrontal cortex (MPC) and amygdala within the context of a model in which the dysfunction of MPC results in the disinhibition of limbic transmission over the amygdala. The dysregulation of neurochemical function, cognitive, endocrine, immune and autonomic systems [19] are critical alterations in the homoeostatic processes capable of causing anxiety and depression. The changes in neuronal processes could result in structural changes, disruption of neural networks and plasticity [20], impairment of neural function and chemical imbalance in the brain.

### Pharmacological treatment of anxiety and depression

Despite the availability of numerous classes of drugs for the treatment of anxiety and depression, full remission of disease symptom has remained elusive. Clinical use of these drugs (*Table I*) is limited by their characteristic side effects and poor tolerability profile. Some of the first-line anxiolytic and antidepressant drugs enhance monoaminergic function by inhibiting the enzyme responsible for the breakdown of monoamines (norepinephrine, serotonin and dopamine) and block reuptake of monoamines to increase their concentration at the synaptic cleft. *Table I* displays several other mechanisms of anti-anxiety and antidepressant properties of drugs.

First-line anxiolytic and/or antidepressant drugs are widely sought after by patients with or without prescription. Benzodiazepines that are the most commonly used anxiolytic drugs potentiate the inhibitory GABAergic transmission [21]. Interestingly, the actions of some anxiolytic drugs with antidepressant activity are an indication that these psychiatric diseases could have overlapping pathophysiology. The action of serotonin agonists such as buspirone and gepirone on presynaptic and postsynaptic 5-hydroxytryptamine-1A ($5\text{-HT}_{1A}$) receptors predicts both anxiolytic and antidepressant activities [22]. Meanwhile, some of the drugs that are currently on the counter seem to be characterized with cases of side effects, for example benzodiazepines which induce sedation, ataxia, and amnesia among others (*Table I*). Despite the advances in the treatment of depression and anxiety, clinical needs of substantial number of patients are yet to be met. The efficacy, duration of effects and side effects of available drugs have constituted serious concern and the need for newer drugs. The diversity in neural targets makes phytomedicine a promising candidate for the treatment of these diseases.

## MEDICINAL PLANTS

### Popular application and therapeutic value of medicinal plants

The use of medicinal plants in the prevention and treatment of diseases has been reported time immemorial [34,35]. The impact generated by the discovery of naturally occurring compounds, such as antibiotics (e.g. penicillin, tetracycline, erythromycin), anticancer drugs (e.g. vinblastine, vincristine, paclitaxel), cardiac glycosides (digoxin), among others, has attracted a lot of interests [36]. Currently, the therapeutic value of medicinal plants is reflected in the percentage of medical prescriptions of which 25% are derived from vegetal species [37]. Across the world, traditional medicine (TM) serves either as the mainstay of healthcare delivery or complement to it [38]. In some countries, TM or nonconventional medicine may be termed complementary and alternative medicine (CAM) which is an important and often underestimated part of health services [39]. TM has a long history of use in health maintenance, disease prevention and treatment. TM is the total sum of knowledge, skill, and cultural practices based on the theories, beliefs and indigenous experiences whether explicable or not towards diagnosis and treatment of physical and mental illness [40].

According to the World Health Organization (WHO) in the guidelines on the conservation of medicinal plants, about three-quarters of the world population depend on TMs for their primary healthcare needs [38]. The integration of CAM and conventional medicine indicates inherent value of CAM in primary healthcare needs [41,42]. In 2008, approximately 38% of American adults (about 4 in 10) and approximately 12% of American children (about 1 in 9) are using some form of CAM. The following year, sales of herbal supplements in the mass market retail channel grew 15% to nearly $900 million representing over 17% of the total $5 billion consumer sales [43]. In 2012, sales of herbal

**Table I** Some drugs with anxiolytic and antidepressant properties [23–33].

| Classes | Drugs | Side effects | Mechanism |
|---|---|---|---|
| Anxiolytic drugs | | | |
| Barbiturate | Amytal | Somnolence, headache, confusion, hyperkinesias, ataxia, etc. | The interaction of barbiturates with $GABA_A$ receptors decreases the rate of dissociation of GABA from these receptors, thereby increasing the duration of the $GABA_A$-activated opening of chloride channels. |
| | Seconal | Dizziness, headache, confusion, bradycardia, ataxia, etc. | |
| | Tuinal | Drowsiness and dizziness, stomach upset, headache, weakness, etc. | |
| | Phenobarbital | Clumsiness, dizziness, excessive daytime drowsiness, etc. | |
| | Nembutal | Confusion, hallucinations, shallow breathing, weak pulse, etc. | |
| BZD | Alprazolam | Confusion, hyperactivity, agitation, hostility, chest pain, etc. | These agents bind to BZD site of $GABA_A$ increasing the frequency of chloride channel opening, thereby potentiating inhibitory effect of GABA. |
| | Clonazepam | Confusion, hallucinations, painful or difficult urination, etc. | |
| | Diazepam | Sedation, dependence, ataxia, amnesia, slurred speech, etc. | |
| | Lorazepam | Drowsiness, sleepiness, fatigue, confusion, amnesia, etc. | |
| Antihistamines | Hydroxyzine | Dizziness, hypotension, constipation, dry mouth, confusion, etc. | Histamine $H_1$ receptor antagonists. |
| | Chlorpheniramine | Constipation, diarrhoea, dizziness, drowsiness, dry mouth, etc. | |
| Azapirone | Buspirone | Dizziness, nausea, insomnia, nervousness, chest pain, etc. | Partial agonist of 5-$HT_{1A}$ receptor. |
| Anxiolytic and antidepressant drugs | | | |
| MAOI | Iproniazid | Sexual dysfunction, drowsiness, dry mouth, itching, hepatitis, etc. | MAO-A and MAO-B inhibition |
| | Isocarboxazid | Faintness, numbness, orthostatic hypotension, photophobia, etc. | MAO-A and MAO-B inhibition |
| | Tranylcypromine | Allergic reaction, tremor, blurred vision, nausea, vomiting, etc. | MAO-A and MAO-B inhibition |
| | Phenelzine | Dizziness, headache, constipation, dry mouth, hyperactive, etc. | MAO-A and MAO-B inhibition |
| | Moclobemide | Irregular heartbeats, blurred vision, high blood pressure, etc. | MAO-A inhibition |
| TCAs | Imipramine | Dizziness, impotence, dry mouth, nightmares, pupil dilation, etc. | Inhibition of 5-HT and NE reuptake by blocking the SERT and NET. |
| | Desipramine | Constipation, diarrhoea, dizziness, dry mouth, weight changes, etc. | |
| | Clomipramine | Drowsiness, dry mouth, headache, irritability, tiredness, etc. | |
| | Amitriptyline | Chest pain, sweating, general ill feeling, numbness, etc. | |
| | Nortriptyline | Agitation, hallucinations, overactive reflexes, confusion, etc. | |
| SSRIs | Fluoxetine | Nausea, vomiting, diarrhoea, sweating, confusion, agitation, etc. | Selective inhibition of 5-HT reuptake |
| | Paroxetine | Sexual dysfunction, heartburn, runny or stuffy nose, etc. | |
| | Sertraline | Decreased appetite or weight loss, diarrhoea or loose stools, etc. | |
| | Citalopram | Sexual dysfunction, sleepiness or unusual drowsiness, etc. | |
| | Fluvoxamine | Constipation, headache, tiredness, sexual dysfunction, etc. | |
| Antagonist/reuptake inhibitor | Nefazodone | Hepatic failure, nausea, blurred vision, postural hypotension, etc. | Blocks 5-$HT_2$ receptors and inhibits neuronal reuptake of 5-HT and NE to prolong their concentration in the synaptic cleft |
| $\alpha_2$-antagonist | Mirtazapine | Agitation, hallucinations, fever, headache, loss of coordination, etc. | Enhances monoaminergic function by presynaptic $\alpha_2$-receptor blockade to disinhibit 5-HT and NE release |
| SNRI | Venlafaxine | Nausea, dry mouth, dizziness, decreased libido, delirium, etc. | Enhances monoaminergic function by inhibiting neuronal reuptake of 5-HT and NE |
| | Duloxetine | Tremors, convulsions, reduced activity, slow pupillary response, etc. | |
| NDRI/ATCA | Amineptine | Acne, nervousness, insomnia, suicidal tendency, etc. | Enhances monoaminergic function by inhibiting neuronal reuptake of DA and NE |
| | Bupropion | Headache, insomnia, dysphoria, seizure, dry mouth, etc. | |

Some of the drugs on this table elicit multiple effects with plural mechanism of action.

dietary supplements in the USA increased by 5.5% [43]. Despite the great potential of medicinal plants as a source of new molecules, there is still a dearth of comprehensive studies. The few studies on these medicinal plants are largely at preliminary stage [44,45].

## Relevance of medicinal plants to the development of psychoactive drugs

Nowadays, there seems to be overdependence on synthetic drugs for curing or alleviating certain emotional disorders. Meanwhile, researches have shown that many people look for herbal products for the treatment of different kinds of psychiatric disorders. In recent times, scientific studies are being focused on the validation of popularly acclaimed medicinal plants with psychoactive properties. Important compounds acting on the central nervous system have been isolated from plant species, and some of them are now being used clinically (in their natural or modified form) for various CNS disorders as shown in *Figure 2* and *Table II*.

In the United States, Cragg and associates conducted an analysis of drugs approved by the Food and Drug Administration (FDA) in the United States during 12-year period (1983–1994) and found that 157 of 520 drugs (30%) approved were natural products or their derivatives [46]. In the expanded version of this study by Newman and colleagues [47] during a 22-year period (1981–2002), it was particularly evident that over 60 and 75% of these drugs in the areas of cancer and infectious diseases, respectively, were of natural origin.

Studies have demonstrated that many phytochemicals such as saponins [48], alkaloids [49,50], polyphenols [51], triterpenoid [52], essential oil [53,54], fatty acid [55], flavonoids [56] possess anxiolytic- and antidepressant-like effects. In this context, it is worth mentioning the discovery of new drugs with anxiolytic and antidepressant activities. During 1981–2002, 10 new chemicals entities with anxiolytic activity and 21 with antidepressant activity were developed from natural or synthetized origin [47].

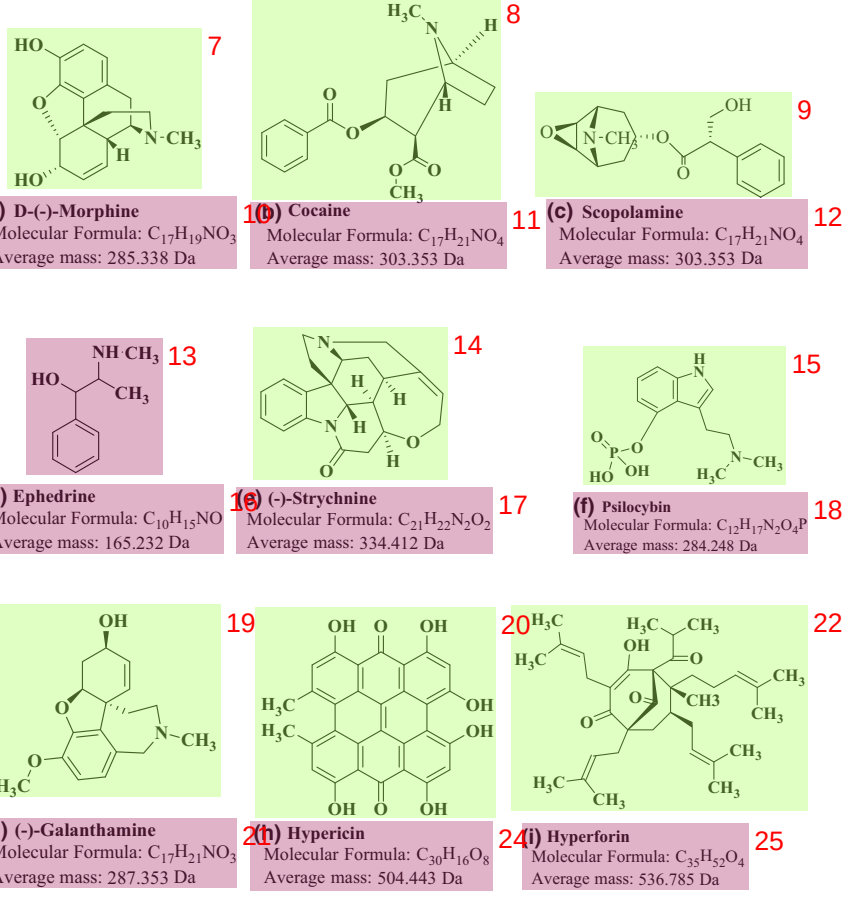


**Figure 2** Some common psychoactive secondary metabolites isolated from medicinal plants.

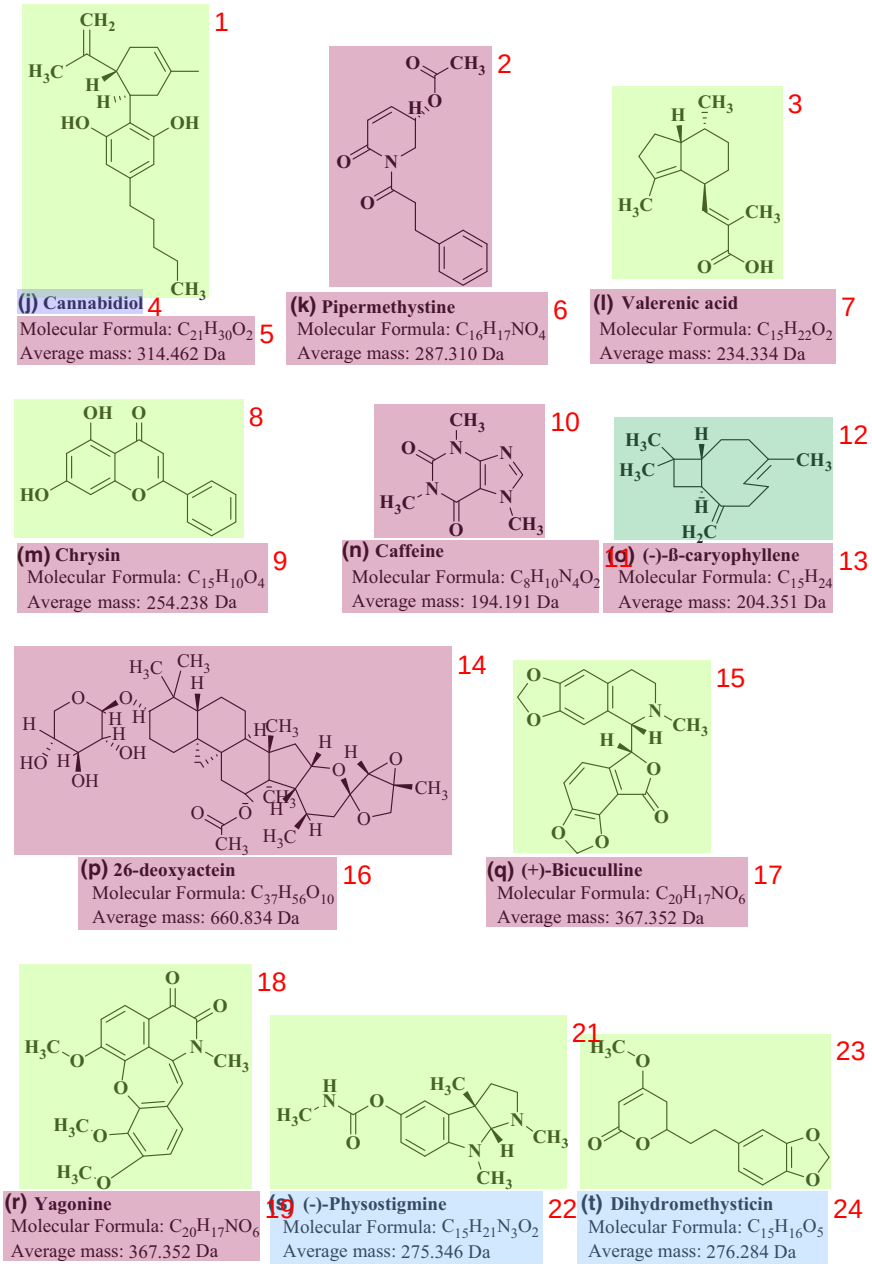


**Figure 2** (Continued)

## Plant species with anti-anxiety and/or antidepressant properties

Regulatory bodies provide definitions for herbal medicinal products. They are those obtained with exclusive use of botanicals with recognized efficacy, acceptable level of safety, scientific data, preclinical (pharmacological and toxicological studies) and clinical publications [57,58]. Some herbal medicines have been approved by regulatory bodies for treating mental disorders. In Brazil, the National Agency of Sanitary Surveillance (ANVISA) included products that are derived from *Passiflora incarnata*, *Piper methysticum*, *Valeriana officinalis*, *Cimicifuga racemosa* for the treatment of anxiety disorders and/or depression. Like ANVISA, European Medicines Agency (EMA) included *Hypericum perforatum* L. (St. John's Wort, SJW), *Melissa officinalis* L. (Melissa leaf), *V. officinalis* L. (Valerian Root) among others in the list of Herbal medicines for the treatment of mental stress and mood disorders [59].

**Table II** Drugs that are isolated from plants with biological activities on the CNS.

| Metabolites | Isolated by | Year |
|---|---|---|
| Morphine | Sertürner | 1805 |
| Strychnine | Pelletier and Caventou | 1818 |
| Caffeine | Friedlieb and Ferdinand Runge | 1819 |
| Cocaine | Albert Niemann | 1859 |
| Physostigmine | Jobst and Hesse | 1864 |
| Scopolamine | Albert Ladenburg | 1881 |
| Ephedrine | Nagai | 1885 |
| Methystine | Pomeranz | 1889 |
| Chrysin | Semrau | 1889 |
| Caryophyllene | Liebig's Annalen | 1892 |
| Yagonine | Reidel | 1904 |
| Dihydromethysticin | Winzheimer | 1908 |
| Bicuculline | Mansk | 1932 |
| Hypericin | Brockmann, Haschad, Maier and Pohl | 1939 |
| Cannabidiol | Adams, Pease and Clark | 1940 |
| Psilocybin | Albert Hoffman | 1943 |
| Galantamine | Mashkovsky | 1951 |
| Valerenic acid | Stoll and Seebeck | 1957 |
| Hyperforin | Gurevich and colleagues | 1971 |
| 27-Deoxyactein | Berger, Junior and Kopanski | 1988 |

## *Hypericum perforatum L.* (SJW)

*Hypericum perforatum* popularly known as SJW is a perennial herb native to Europe [60]. This species has been studied extensively and described in 'American Herbal Pharmacopoeia TM, Therapeutic Compendium™ and in American Botanical Council'. The herbal medicines derived from *H. perforatum* are prescribed around the world for moderate depressive states, anxiety and other disorders of CNS [61]. Hypericin and hyperforin have been associated with the effect of *H. perforatum*. Many researchers suggested that hypericin which inhibits MAO-A and MAO-B enzymes with strong affinity for sigma receptors to regulate dopamine levels is the constituent of SJW that is responsible for antidepressant activity of this species [61]. In addition, hyperforin isolated from SJW contributes to the extract's effects on afferent excitability and neurotransmission. This compound enhances the extracellular levels of serotonin, dopamine, noradrenaline, GABA and L-glutamate [62,63]. It is thought that hyperforin activates nonselective cation transient receptor potential (TRP) channel TRPC6 to increase intracellular sodium and calcium content, thereby reducing neurotransmitter reuptake [64,65]. Many clinical studies have shown antidepressant activity of *H. perforatum* [66–69]. However, there are great controversies between the results presented. This may be due to different inclusion criteria, sample size and doses of standardized extract. All these variables jointly contribute to the lack of consensus among researchers regarding the use of herbal derivatives from *H. perforatum*.

## *Passiflora incarnata* L. (Passion flower)

The herbal medicines derived from *P. incarnata* are prescribed in many parts of the world to treat some CNS disorders. This plant is used for the treatment of insomnia and anxiety disorders in Brazil, Europe and USA [57,70]. Clinical applications of this species worldwide have led to its inclusion in British Herbal Pharmacopoeia (1983), Homoeopathic Pharmacopoeia of India (1974), United States Homoeopathic Pharmacopoeia (1981), Pharmacopoeia Helvetica (1987), and in the pharmacopoeia of Egypt, France, Germany and Switzerland [71]. Phytochemical studies of *P. incarnata* showed the presence of flavonoids (orientin, isoorientin, vitexin, isovitexin and chrysin), cyanogenic glycosides and indole alkaloids [72,73]. Zanoli et al. [74] and Brown et al. [75] reported the anxiolytic-like effect of chrysin in rats, which might be due a benzodiazepine receptors ligand [76]. However, the anxiolytic effects of *P. incarnata* do not seem to be associated solely chrysin or another compound, but it seems associated with phytocomplex (different phytoconstituents) acting in a synergistic manner [70].

## *Piper methysticum* G. Foster (Kava)

Regulatory bodies of herbal medicines have included *P. methysticum* G. Foster (kava) for the symptomatic treatment of mild-to-moderate stages of anxiety [77]. This species has also been indicated for depression, anxiety, insomnia and attention deficit/hyperactivity disorder comorbid [78]. Kava is a South Pacific plant with traditional application as an anxiolytic. Kavalactones (or kavapyrones) such as kawain, dihydrokavain, methysticin, dihydromethysticin and yangonin are among bioactive compounds found in Kava [79] . Recent studies on the mechanisms of action for isolated kavalactones have revealed activities on 38/nuclear factor-kappaB/cyclo-oxygenase 2 signalling pathway [80]. Kava produces blockade of voltage-gated ion channels, wherein methysticin and kavain bind to sodium channel in its inactivated state and prolong its inactivation [81]. Kavalactones also inhibit MAO-B [82] and blocked the *in vitro* uptake of noradrenaline into synaptosomes prepared from the cerebral cortex and the hippocampus of the rat [83]. In addition, Wu et al. [84] showed inhibitory activities of COX-1 and COX-2 from the dihy-

drokavain and yangonin. A clinical study carried out in 1996 by Lehmann and collaborators [85] had demonstrated the efficacy of Kava extract vs. placebo in patients with states of anxiety. In 2013, Sarris et al. [86] also showed a significant reduction in anxiety for the kava group compared with the placebo group. However, in recent years several reports indicate possible hepatotoxicity associated with kava [87].

### *Valeriana officinalis* L. (Valerian)

*Valeriana officinalis* possesses moderate sedative and sleep-promoting effect. It is being used in the treatment of sleep and anxiety disorders [88–90]. The use of Radix Valerianae is described in the World Health Organization Monographs on Selected Medicinal Plants (1999), European Pharmacopoeia (1998), American Herbal Pharmacopoeia (1999) and European Medicines Agency (2006) as a mild sedative and sleep-promoting agent in addition to the treatment of nervous excitation and anxiety-induced sleep disturbances [91–94]. In UK, at least 25 products contain valerian and over 400 products in Germany contain this compound [95]. The anxiolytic activity of valerian has been associated with the presence of some monoterpenes and sesquiterpenes [96]. Valerenic acid and valerenol enhance the response to multiple types of recombinant $GABA_A$ receptors [97,98]. Many clinical trials on the efficacy of valerian extract have shown its potential for the treatment of sleep and anxiety disorders [90,99,100].

### *Cimicifuga racemosa* L. (Nutt.) Black cohosh

Regulatory bodies have included the use of *C. racemosa* L. (Nutt.) for depressive mood swings among other indications [57,101–103]. Several studies on *C. racemosa* (black cohosh) have reported its application for menopause-related anxiety disorder [104,105]. The standard extract of *C. racemosa* contains triterpene glycosides (cimicifugoside, 23-epi-26-deoxyactein and actein), aromatic acids (salicylic acid and ferulic acid), tannins, resins, phytosterols and fatty acids. Recently, $N_\omega$-methylserotonin was identified in the roots/rhizomes of *C. racemosa* as a potent agonist of serotonin 5-$HT_{1A}$ and 5-$HT_7$ receptors [106]. Despite the extensive use of *C. racemosa* especially during menopause, clinical studies did not show significant anxiolytic effect of black cohosh as compared to placebo. The small sample size, choice of black cohosh preparation and dose used may have been the limiting factors in these studies [107].

### *Pimenta pseudocaryophyllus* (Gomes) l.R. Landrum: from popular reports to the bench

*Pimenta pseudocaryophyllus* popularly known as pau-cravo, louro-cravo, louro, craveiro among others [108,109] remains one of the classical examples of plant species in recent time that was carefully selected on the basis of its folkloric application as a calming agent and nerve tonic [110–114]. Collection, identification and preparation of organic leaf extract of this species were followed by isolation of secondary metabolites [108] prior to chemical modifications [115]. General pharmacological test was conducted to verify behavioural alterations, determine appropriate route of administration, estimate dose and potential toxic effects of the ethanolic leaf extract on the animals [116]. The crude extract shows CNS activity [116]. The crude extract was partitioned with increasing polarity of solvent to obtain Hexane, dichloromethane (DF), ethyl acetate and aqueous fractions [117]. The fractions were subjected to pharmacological screening [open field, light–dark box (LDB), elevated plus maze (EPM), tail suspension and forced swimming test (FST)] as described above. The DF which showed the most promising anxiolytic- and/or antidepressant-like activities was further investigated for possible mechanisms of actions that are involved.

Considering the anti-anxiety and antidepressant-like activities of DF, the fraction was subjected to further phytochemical analysis. Oleanolic acid and methyl isoeugenol among others were isolated [116]. These isolates demonstrated antidepressant-like activities in male Swiss albino mice [7]. The plurality of biological activities and mechanism of oleanolic acids are considered to be limiting factors to its therapeutic application [7,118,119]. Meanwhile, susceptibility of this triterpene to chemical modification makes it an important substrate for the development of new drug with potential anti-anxiety and antidepressant. Oleanolic acid acrylate, methacrylate, methyl fumarate and ethyl fumarate were synthesized through a single-step esterification of oleanolic acid with appropriate acyl chloride [115]. These oleanolic acid derivatives were subjected to open field and FSTs. Oleanolic acid acrylate elicits antidepressant-like effect [115]. Together, the ethnopharmacological survey and preclinical data on the crude extract, fractions and isolates of *P. pseudocaryophyllus* demonstrate strategic planning towards the development of phytomedicine with anxiolytic and/or anti-anxiety property (ies).

**Table III** Summarized information about medicinal plants used for the treatment of anxiety and/or depression.

| Medicinal plants | Occurrence | Popularly acclaimed effect and preparation | Medical prescription | Mechanism of action | Active principles | Limitations/side effects |
|---|---|---|---|---|---|---|
| Melissa officinalis L. (Lamiaceae) | Mediterranean region [120], Western Asia [121], south-western Siberia and Northern Africa [122]. It is also cultivated worldwide [122,123] | Memory-enhancing properties, mild sedative and sleep aid [124,125]. Treatment of depression and nervous tension [126] | Treatment for benign palpitations, and as a promising anxiolytic drug [127] | Inhibitor of rat brain GABA transaminase [123,124,128] | Rosmarinic acid and the triterpenoids, ursolic acid and oleanolic acid [128] | Without side effects or symptoms of toxicity [129] |
| *Cimicifuga racemosa* L. Nutt (Ranunculaceae) | North America; Georgia, North to Ontario and West to Arkansas and Wisconsin [130] | Treatment of general malais, nervous disorders, uterine disorders, as well as to facilitate intermittent uterine contractions during labour [130] | Treatment of symptoms of menopause, anxiety and depression [130,131] | Act in the hypothalamus vasomotor centre. Other in vivo and in vitro studies indicate a dopaminergic effect [132] | Triterpenes and derivatives of flavones [132] | Concomitant administration with any type of medication should be avoided because of the possibility of increasing the bioavailable concentration of drugs in the blood. This is due the suppression of CYP3A4 by *Cimicifuga racemosa* [133] |
| *Litsea glaucescens* (Lauraceae) | Mexico and Central America [134] | Treatment of illnesses related to the central nervous system [135] | | Interaction with the serotonergic 5-$HT_{1A}$ receptors, $\alpha_2$- and β-adrenoceptors and dopaminergic receptors $D_1$ [134] | Linalool and β-pinene [134] | |
| *Hypericum perforatum* L (Hypericaceae) | Europe, but occurs in Asia, Northern Africa and North America [61,136] | Treatment of neuralgia, mood disorders as anxiety, neurosis and mild-to-moderate depression [136] | Treatment of anxiety, depression and insomnia [137] | Selective inhibitor of MAO-A and MAO-B; Inhibition of 5-HT, NE and DA uptake; antagonist of NMDA receptors; moderate interactions with the $GABA_A$ receptor [136]. Suppression of the release of interleukin 6 [137] | Hypericin and hyperforin [61,137] | Induction of the metabolism of coadministered medications because it may potentiate certain enzymes of the cytochrome P450 [136] |

**Table III. Continued**

| Medicinal plants | Occurrence | Popularly acclaimed effect and preparation | Medical prescription | Mechanism of action | Active principles | Limitations/side effects |
|---|---|---|---|---|---|---|
| *Lavandula angustifolia* Mill. (Lamiacae) | Mediterranean regions, the islands of the Atlantic, Turkey, Pakistan, India, Northern and Southern Africa, Micronesia, the Arabian Peninsula, Bulgaria and Russia [138] | Treatment of tension, nervous disorders, anxiety and depression [138,139] | Treatment of depression [138,139] | Anxiolytic-like effect likely through 5-$HT_{1A}$ receptors [140] | Linalool and linalyl acetate [172,173] | Allergic reactions. Limitations during other illnesses or in patients with specific organ dysfunction. Interactions with other herbs or pharmaceuticals [138] |
| *Pimenta pseudocaryophyllus* (Gomes) L.R. Landrum (Myrtaceae) | Brazil [116] | Soothing effect, a diuretic and aphrodisiac agent [116]. Calming agent and nerve tonic [110] | | Anxiolytic-like activity that involves 5-$HT_{1A}$ receptor [116] | (E)-methyl isoeugenol and oleanolic acid [116] | The plurality of biological activities and mechanism of oleanolic acids are considered to be limiting factors to its therapeutic application [7,118,119,141,142] |
| *Mimosa pudica* (Fabaceae) | Brazil [143] | Treatment of depression and insomnia (the infusion of dried leaves) [144] | | The antidepressant-like effect is mediated by the serotonergic system [144] | Norepinephrine, d-pinitol, b-sitosterol, mimosine [145] | |
| *Annona cherimola* Mill.(Annonaceae) | Ecuador, Peru, Northern South America and Central America [146] | Anti-anxiety, anticonvulsant and tranquilizing properties [147] | | Antidepressant-like effect through increase in monoaminergic neurotransmission [147] | Liriodenine, anonaine and nornuciferine [147] | |
| *Tagetes lucida* Cav. (Asteraceae) | México and Central America [148] | Stimulant of the immune system, anti-anxiety, antidepression [148,149] | | The antidepressant-like effect is mediated by 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors [148] | Quercetin [148], gallic acid, caffeic acid [149] | Diarrhoea, pain, palpebral ptosis, piloerection and tearing) [149] |
| *Agastache mexicana* subsp. *Mexicana* (Lamiaceae) | Asia and North America [150] | To relief nervous condition and as tranquilizer [150] | | The anxiolytic-like effect of the tilianin, as one of the major constituents in *A. mexicana* is mediated by the $GABA_A$/BZDs, receptor [151] | Acacetin-7-O-glucoside (tilianin), acacetin-7-O-β-d-(6″-O-malonyl)–glucoside; luteolin-7-O-β-d-(6″-O-malonyl)–glucoside [150] | |
| *Agastache mexicana* subsp. *Xolocotziana* (Lamiaceae) | Asia and North America [150] | To relief nervous condition and as tranquilizer [150] | | GABAergic activity is involved in the anxiolytic-like effect of tilianin, one constituent of the *A. mexicana* [152] | Acacetin-7-O-glucoside (tilianin), diosmetin-7-O-β-d-(6″-O-malonyl)–glucoside; [150] | |

**Table III. Continued**

| Medicinal plants | Occurrence | Popularly acclaimed effect and preparation | Medical prescription | Mechanism of action | Active principles | Limitations/side effects |
|---|---|---|---|---|---|---|
| *Passiflora incarnata* | North America [70] | Treatment of anxiety disorder, insomnia [57] | Treatment of generalized anxiety disorder (GAD) [70], precocious menopause symptoms, insomnia, depression, anger and headaches [153] | Agonist of the $GABA_A$ and $GABA_B$ receptors [70] | Orientin, isoorientin, vitexin, isovitexin and chrysin [72,70,73] | Severe nausea, vomiting, drowsiness, prolonged QT and episodes of nonsustained ventricular tachycardia [70] |
| *Piper methysticum* G. Foster | South Pacific [79] | Treatment of depression, anxiety, insomnia and attention deficit/hyperactivity disorder comorbid [78] | Treatment of anxiety [85,86] | Kavalactones inhibit MAO-B [82] and blocked the in vitro uptake of noradrenaline [83] | Kawain, dihydrokavain, methysticin, dihydromethysticin and yangonine [79] | Possible hepatotoxicity [87] |
| *Valeriana officinalis* L. | Europe, Asia and North America [154] | Treatment of sleep and anxiety disorders [88–90] | Treatment of sleep and anxiety disorders [90,99,100] | Valerenic acid and valerenol enhance the response to multiple types of recombinant $GABA_A$ receptors [97,98] | Valerenic acid and valerenol [97,98] | Large doses are known to cause withdrawal symptoms. Continuous use may result in dependency [154] |

*Table III* presents information about some species of medicinal plants used for treatment of anxiety and/or depression, highlighting aspects of the occurrence, ethnopharmacology, mechanisms of action of the extract or phytochemicals and medical prescriptions, when applicable.

## Evaluation of putative anxiolytic effects of medicinal plants

Animal models play a central role in all areas of biomedical research. To investigate anxiolytic effect of crude extract or active principles from medicinal plants, a wide range of behavioural testing has been developed [155–157]. Some well-established tests of anxiety include open field test. This test was originally introduced as a measure of emotional behaviour in rats and later adapted to mice [158–160]. Parameters such as ambulation, time and crossing at the centre of the open field, grooming, freezing and rearing are often measured. Light–dark box (LDB) has also been used to investigate anxiolytic properties. The underlining principle of LDB model is based on the aversion of rodents to brightly illuminated areas, novel environment and light-induced mild stress [161,162]. The number of transitions between the two compartments and the time spent in the light area are recorded over a specified period [156]. Elevated plus maze is another widely used behavioural model with a strong predictive validity to measure the anxiolytic-like effect of a novel compound [163–166]. The time spent and the number of entries with all four paws inside the open arms are well-established parameters for assessing anxiolytic or anxiogenic property of new drugs. The open and closed arms are considered to evoke the same exploratory drive; therefore, avoidance of the open arms is considered to be a result of the induction of higher levels of fear [164]. Other models such as marble-burying [167] and hole board tests with repetitive tendency have been used to evaluate anxiolytic- or anxiogenic-like effects.

## Evaluation of putative antidepressant effects of medicinal plants

Forced swimming test is the most widely used pharmacological test for assessing antidepressant activity [168]. The FST involves the scoring of active (swimming and climbing) or passive (immobility) behaviour. Reduction in immobility is interpreted as an antidepressant-like effect [169] of the extracts/compounds being tested provided it does not increase general locomotor activity, which could provide a false-positive result (as in the case of stimulant) in the FST. Tail suspension test (TST) is another highly validated test for the investigation of antidepressant-like property of drugs [170]. Like antidepressant drugs, psychostimulants also reduce immobility in this model. The TST shares a similar basic principle with FST in that animals develop an immobile posture when placed in an inescapable stressful situation after initial escape-oriented movements. Acute administration of an antidepressant drug prior to the exposure of the experimental subject to the TST prolonged active escape-directed behaviours [171].

## CONCLUSIONS

Current pharmacological approaches to the management of anxiety and depression are yet to engender desirable results in clinical practice. Some of the first-line and new medications that apparently fall into the existing classes of drugs are still associated with side effects. Medicinal plants provided ample opportunities for the development of anti-anxiety and antidepressant drugs. The acceptance of herbal medicines for the treatment of these mental disorders has grown as a result of the improvements in their quality. Standardization of extracts and plant isolate, adequate scientific data on safety and efficacy, preservation of medicinal plant's diversity, appropriate legislation and regulatory agencies are still critical steps to the development of anti-anxiety and antidepressant phytomedicine.

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## CONFLICTS OF INTEREST

The authors have no conflict of interests to declare.

## ABBREVIATIONS

5-HT – 5-hydroxytryptamine
ANVISA – Agency of Sanitary Surveillance
ATCA – atypical tricyclic antidepressants
BZD – benzodiazepine
CNS – central nervous system
CAM – complementary and alternative medicine
DA – dopamine
DF – dichloromethane fraction

EMA – European Medicines Agency
FDA – Food and Drug Administration
FST – forced swimming test
GABA – γ-aminobutyric acid
MAOI – Monoamine oxidase inhibitor
MPC – medial prefrontal cortex
NDRI – norepinephrine–dopamine reuptake inhibitor
NE – norepinephrine
NET – norepinephrine transporter
SERT – serotonin transporter
SNRI – serotonin–norepinephrine reuptake inhibitor
SSRI – selective serotonin reuptake inhibitor
SJW – St. John's Wort
TST – tail suspension test
TCA – tricyclic antidepressants
TM – traditional medicine
TRP – transient receptor potential
WHO – World Health Organization

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