

**REVIEW
ARTICLE**

Treatment of anxiety and depression: medicinal plants in retrospect

James O. Fajemiroye, Dayane M. da Silva*, Danillo R. de Oliveira, Elson A. Costa

Department of Pharmacology, Institute of Biological Sciences, Federal University of Goiás, 74001-970, Goiânia, GO, Brazil

Keywords

anxiety
depression
medicinal plants
Pimenta pseudocaryophyllus
preclinical models

Received 22 September 2015;
revised 8 January 2016;
accepted 2 February 2016

*Correspondence and reprints:
daymoress@gmail.com

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 This review was conducted through bibliographic investigation of scientific journals, books, electronic sources, unpublished theses and electronic medium such as ScienceDirect and PubMed.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. In spite 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.

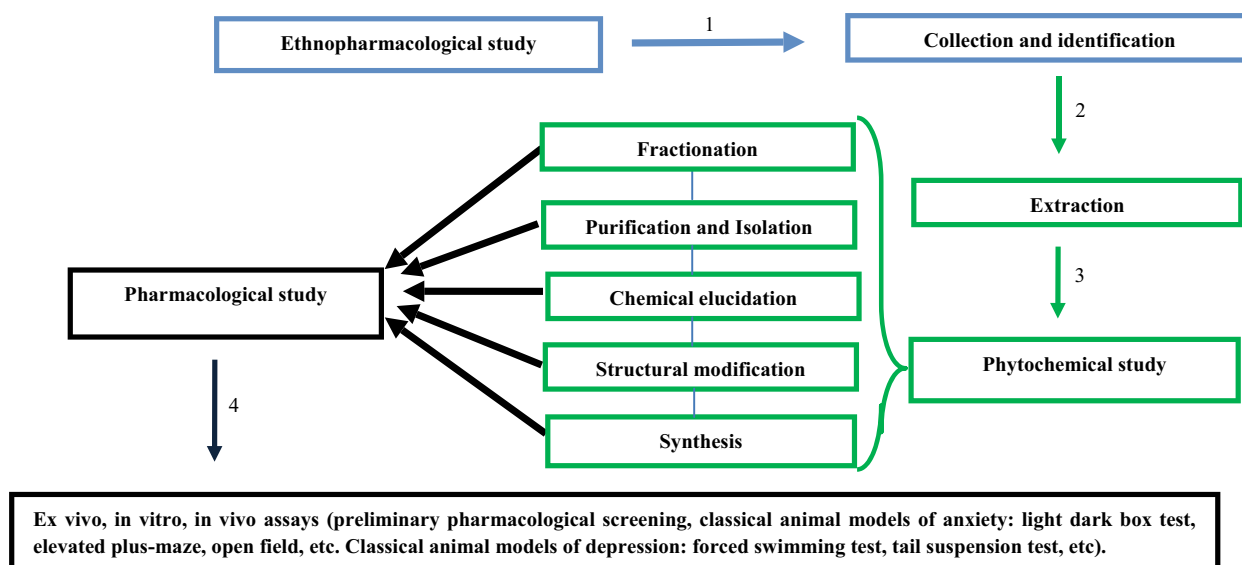


Figure 1 Hypothetical model for the discovery of medicinal plant extracts and phytoconstituents with anxiolytic and/or antidepressant property (ies). (i) Selection of medicinal plant with anxiolytic and/or antidepressant potential based on local reports; (ii) Preparation of standard crude extracts; (iii) 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 homeostatic 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-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 1 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. | |
| | Tranylcypromine | Allergic reaction, tremor, blurred vision, nausea, vomiting, etc. | |
| | Phenelzine | Dizziness, headache, constipation, dry mouth, hyperactive, etc. | |
| | Moclobemide | Irregular heartbeats, blurred vision, high blood pressure, etc. | |
| 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 |
| α_2 -antagonist | Mirtazapine | Agitation, hallucinations, fever, headache, loss of coordination, etc. | Enhances monoaminergic function by presynaptic α_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. | |
| NDR/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 synthesized origin [47].

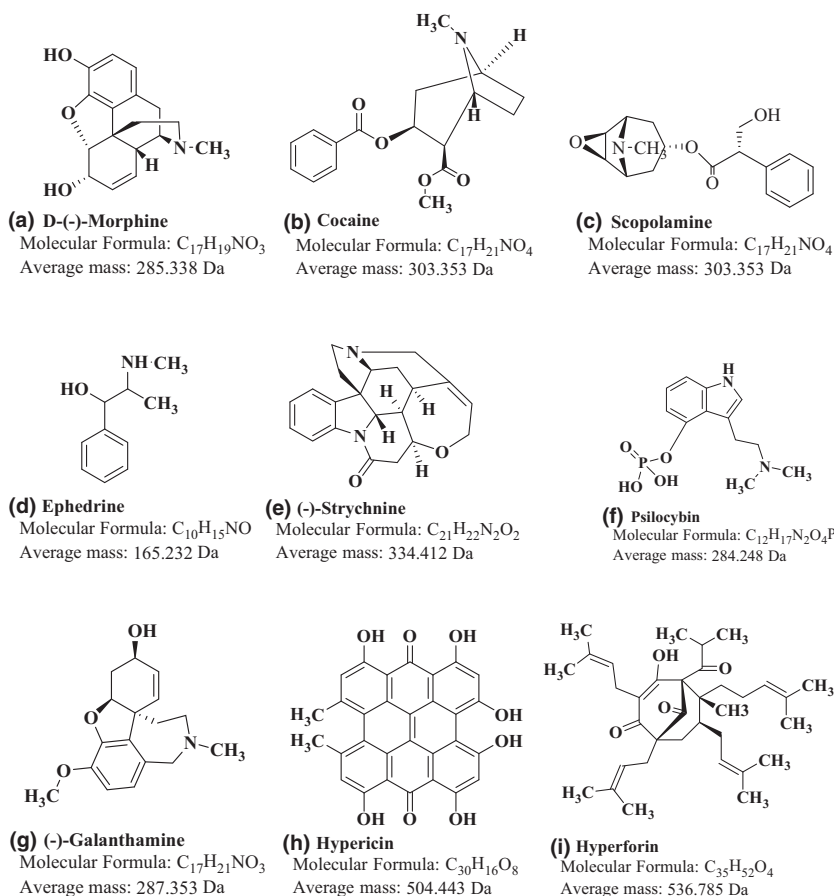


Figure 2 Some common psychoactive secondary metabolites isolated from medicinal plants.

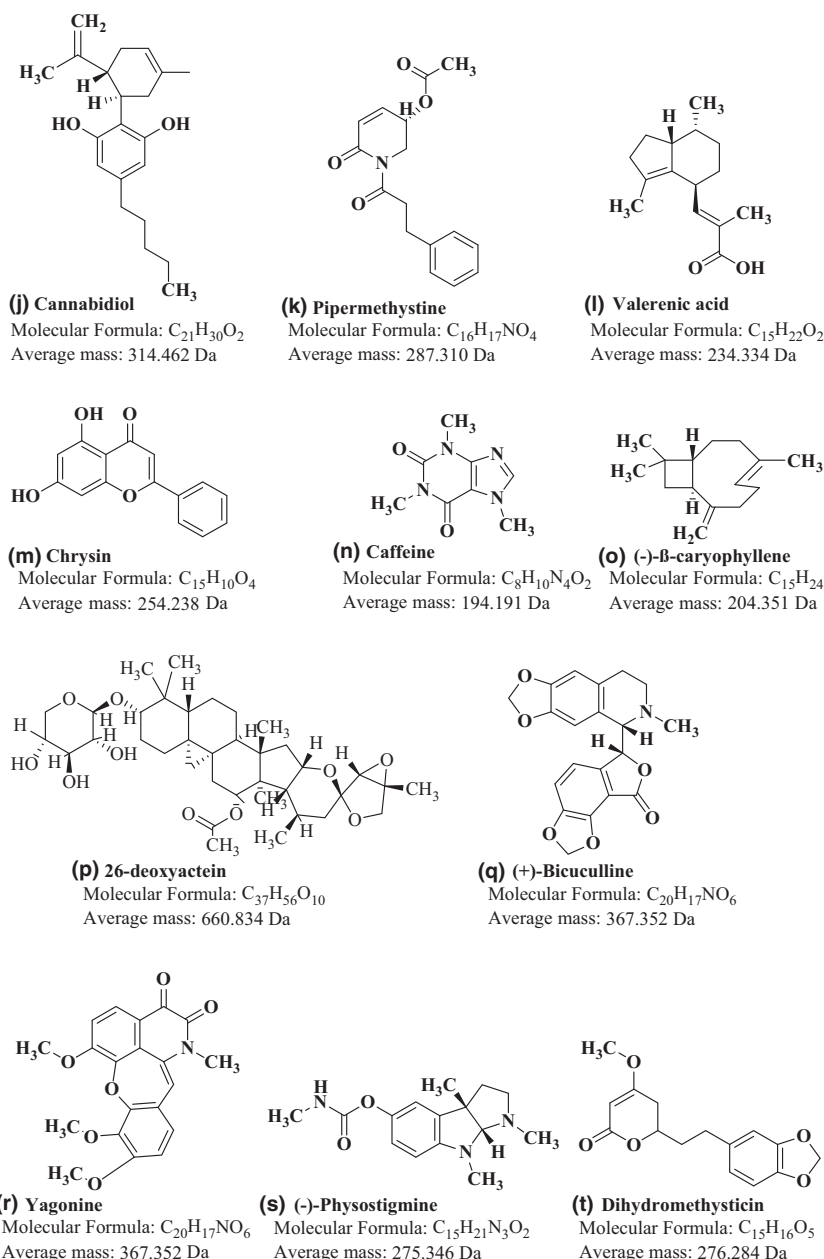


Figure 2 (Continued)

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_ω*-methylserotonin was identified in the roots/rhizomes of *C. racemosa* as a potent agonist of serotonin 5-HT_{1A} and 5-HT₇ 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) I.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 phyto-medicine 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 |
|--|--|---|---|--|--|--|
| <i>Melissa officinalis</i> 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] |
| <i>Cimicifuga racemosa</i> 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 to the suppression of CYP3A4 by <i>Cimicifuga racemosa</i> [133] |
| <i>Litsea glaucescens</i> (Lauraceae) | Mexico and Central America [134] | Treatment of illnesses related to the central nervous system [135] | | Interaction with the serotonergic 5-HT _{1A} receptors, α_2 - and β -adrenoceptors and dopaminergic receptors D ₁ [134] | Linalool and β -pinene [134] | |
| <i>Hypericum perforatum</i> 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 |
|--|---|--|-----------------------------------|---|---|--|
| <i>Lavandula angustifolia</i> Mill. (Lamiaceae) | 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] |
| <i>Pimenta pseudocaryophyllus</i> (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] |
| <i>Mimosa pudica</i> (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] | |
| <i>Annona cherimola</i> 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 normuciferine [147] | |
| <i>Tagetes lucida</i> Cav. (Asteraceae) | México and Central America [148] | Stimulant of the immune system, anti-anxiety, antidepressant [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] |
| <i>Agastache mexicana</i> subsp. <i>Mexicana</i> (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 <i>A. mexicana</i> 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] | |
| <i>Agastache mexicana</i> subsp. <i>Xolocotziana</i> (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 <i>A. mexicana</i> [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 |
|---------------------------------------|--------------------------------------|---|--|--|--|---|
| <i>Passiflora incarnata</i> | 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] | Orientein, isoorientin, vitexin, isovitexin and chrysin [72,70,73] | Severe nausea, vomiting, drowsiness, prolonged QT and episodes of nonsustained ventricular tachycardia [70] |
| <i>Piper methysticum</i> 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 yanguonine [79] | Possible hepatotoxicity [87] |
| <i>Valeriana officinalis</i> 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.

ACKNOWLEDGEMENTS

The authors thank FAPEG, CAPES and CNPq for the study fellowship.

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

REFERENCES

- 1 Ferry S., Baltassat-Millet F. La prospection des plantes medicinales. Lyon Pharmaceutique. (1997) **28** 257–260.
- 2 Soejarto D.D. Biodiversity prospecting and benefit-sharing: perspectives from the field. *J. Ethnopharmacol.* (1996) **51** 1–16.
- 3 Williamson E.M., Okpako D.T., Evans F.J. Selection, preparation and pharmacological evaluation of plant material. *J. Med. Chem.* (1996) **40** 1559–1559.
- 4 Albuquerque U.P., Hanazaki N. As pesquisas etnológicas na descoberta de novos fármacos de interesse médico e farmacêutico: fragilidades e perspectivas. *Rev. Bras. Farmacogn.* (2006) **16** 678–689.
- 5 Cryan J.F., Sweeney F.F. The age of anxiety: role of animal models of anxiolytic action in drug discovery. *Br. J. Pharmacol.* (2011) **164** 1129–1261.
- 6 Overstreet D.H. Modeling depression in animal models. *Methods Mol. Biol.* (2012) **829** 125–144.
- 7 Fajemiroye J.O., Galdino P.M., Florentino I.F. et al. Plurality of anxiety and depression alteration mechanism by oleanolic acid. *J. Psychopharmacol.* (2014) **28** 923–934.
- 8 Seligman M.E.P., Walker E.F., Rosenhan D.L. *Abnormal psychology*. W.W. Norton & Company, New York, 2001.
- 9 Smith M. *Anxiety Attacks and Disorders: Guide to the Signs, Symptoms, and Treatment Options*. In: Help Guide website. 2008. [Online] 2009. www.helpguide.org/mental/anxiety_types_symptoms_treatment.htm (accessed 3 March 2009).
- 10 Mauro V.M., Murray B.S. Quality of life in individuals with anxiety disorders. *Am. J. Psychiatry* (2000) **157** 669–682.
- 11 CMU Institute. Treating depression and anxiety in primary care. *Prim Care Companion J. Clin. Psychiatry*. (2008) **10** 145–152.
- 12 Lopez A.D., Murray C.J. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990–2020 and projected to 2020. Harvard University Press, Boston, MA, 1996.
- 13 Diagnostic and statistical manual of mental disorders, 4th edn, Text Revision DSM-IV-TR, American Psychiatric Association, USA, 2000.
- 14 Nestler E.J., Barrot M., DiLeone R.J., Eisch A.J., Gold S.J., Monteggia L.M. Neurobiology of depression. *Neuron* (2002) **34** 13–25.
- 15 Wayne C.D., Joseph L.P., Maura L.F. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct. Funct.* (2008) **213** 93–118.
- 16 Duman R.S., Monteggia L.M. A neurotrophic model for stress-related mood disorders. *Biol. Psychiatr.* (2006) **59** 1116–1127.
- 17 Palazidou E. The neurobiology of depression. *Br. Med. Bull.* (2012) **101** 127–145.
- 18 Drevets W.C. Orbitofrontal cortex function and structure in depression. *Ann. N. Y. Acad. Sci.* (2007) **1121** 499–527.
- 19 McEwen B.S., Gianaros P.J. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann. N. Y. Acad. Sci.* (2010) **1186** 190–222.
- 20 Castrén E. Is mood chemistry? *Nat. Rev. Neurosci.* (2005) **6** 241–246.
- 21 Tatarczynska E., Koodzinaska A., Chojnacka-Wojcik E. et al. Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. *Br. J. Pharmacol.* (2001) **132** 1423–1430.
- 22 Schechter L.E., Ring R.H., Beyer C.E. et al. Innovative approaches for the development of antidepressant drugs: current and future strategies. *NeuroRx* (2005) **2** 590–611.
- 23 Moreno R.A., Moreno D.H., Soares M.B.M. Psicofarmacologia de antidepressivos. *Rev. Bras. Psiquiatr.* (1999) **21** 24–40.
- 24 Bezchlibnyk-Butler K.Z., Jeffries J.J. *Clinical handbook of psychotropic drugs*, 9th edn. Hogrefe & Huber Publishers, Toronto, Canada, 1999.
- 25 Kennedy S.H., Lam R.W., Cohen N.L., Ravindran A.V., CANMAT Depression Work Group. Clinical guidelines for the treatment of depressive disorders. Medication and other biological treatments. *Can. J. Psychiatry* (2001) **46** 38–58.
- 26 Ravindran L.N., Stein M.B. The pharmacologic treatment of anxiety disorders: a review of progress. *J. Clin. Psychiatry* (2010) **71** 839–854.
- 27 Maxwell R.A., Eckhardt S.B. Iproniazid. *Drug Discovery*. (1990) **615** 143–154.
- 28 Turcotte J.E., Debonnel G., Montigny C., Hebert C., Blier P. Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects. *Neuropsychopharmacology* (2001) **24** 511–521.
- 29 Stahl S.M. Basic psychopharmacology of antidepressants, pt 1: antidepressants have seven distinct mechanisms of action. *J. Clin. Psychiatry* (1998) **59** 5–14.
- 30 Baldessarini R.J. Drugs and the treatment of psychiatric disorders: depression and anxiety disorders, in: Hardman

- J.G., Limbird L.E. (Eds), Goodman & Gilman's the pharmacological basis of therapeutics, McGraw-Hill, New York, NY, 2001, pp. 447–483.
- 31 Stahl S.M. Essential psychopharmacology, 2nd edn. Cambridge University Press, New York, NY, 2000.
 - 32 Stahl S.M., Pradko J.F., Haight B.R., Modell J.G., Rockett C.B., Coughlin S.L.A. Review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim. Care Companion J. Clin. Psychiatry.* (2004) **6** 159–166.
 - 33 Serzone [package insert]. Bristol-Myers Squibb Company, Princeton, NJ, 2002.
 - 34 Fakim G.A. Medicinal plants: traditions of yesterday and drugs of tomorrow. *Mol. Aspects Med.* (2006) **27** 1–93.
 - 35 Jaric S., Mitrovic M., Djurdjevic L. et al. Phytotherapy in medieval Serbian medicine according to the pharmacological manuscripts of the Chilandar Medical Codex (15–16th) centuries. *J. Ethnopharmacol.* (2011) **137** 601–619.
 - 36 Katiyar C., Gupta A., Kanjilal S., Katiyar S. Drug discovery from plant sources: an integrated approach. *Ayu* (2012) **33** 10–19.
 - 37 Duke J.A. Medicinal plants and the pharmaceutical industry, in: Janick J., Simon J.E. (Eds), *New crops*. New York, Wiley, 1993, pp. 664–669.
 - 38 World Health Organization (WHO). WHO Traditional Medicine Strategy (2013) **54** 2014–2023.
 - 39 Hornik-Lurie T., Cwikel J., Feinson M.C., Lerner Y., Zilber N. Use of unconventional therapies by primary care patients – religious resources vs. complementary or alternative medicine services. *Complement. Ther. Med.* (2013) **1** 517–524.
 - 40 Dias A.D., Urban S., Roessner U. A historical overview of natural products in drug discovery. *Metabolites* (2012) **2** 303–336.
 - 41 Gilani A.H., Rahman A.U. Trends in ethnopharmacology. *J. Ethnopharmacol.* (2005) **100** 43–49.
 - 42 Templeman K., Robinson A. Integrative medicine models in contemporary primary health care. *Complement. Ther. Med.* (2011) **19** 84–92.
 - 43 Lindstrom A., Ooyen C., Lynch M.E., Blumenthal C. Herb supplement sales increase 5.5% in 2012: herbal supplement sales rise for 9th consecutive year; turmeric sales jump 40% in natural channel. *Herbal Gram.* (2013) **99** 60–65.
 - 44 Rates S.M.K. Plants as a source of drugs. *Toxicon* (2001) **39** 603–613.
 - 45 Cragg G.M., Newman D.J. Medicinals for the millenia the historical record. *Ann. N. Y. Acad. Sci.* (2001) **953** 1–25.
 - 46 Cragg G.M., Newman D.J., Snader K.M. Natural products in drug discovery and development. *J. Nat. Prod.* (1997) **60** 52–60.
 - 47 Newman D.J., Cragg G.M., Snader K.M. Natural products as sources of new drugs over the period 1981–2002. *J. Nat. Prod.* (2003) **66** 1022–1037.
 - 48 Dang H., Chen Y., Liu X., Wang L., Jia W., Wang Y. Antidepressant effects of ginseng total saponins in the forced swimming test and chronic mild stress models of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* (2009) **33** 1417–1424.
 - 49 Li H.T., Wu H.M., Chen H.L., Liu C.M., Chen C.Y. The pharmacological activities of (-)-Anonaine. *Molecules* (2013) **18** 8257–8263.
 - 50 Liu M., Huang H.H., Yang J. et al. The active alkaloids of *Gelsemium elegans* Benth. are potent anxiolytics. *Psychopharmacology* (2013) **225** 839–851.
 - 51 Sasaki K., El Omri A., Kondo S. *Rosmarinus officinalis* polyphenols produce anti-depressant like effect through monoaminergic and cholinergic functions modulation. *Behav. Brain Res.* (2013) **238** 86–94.
 - 52 Machado D.G., Neis V.B., Balen G.O. Antidepressant-like effect of ursolic acid isolated from *Rosmarinus officinalis* L. in mice: evidence for the involvement of the dopaminergic system. *Pharmacol. Biochem. Behav.* (2012) **103** 204–211.
 - 53 Galdino P.M., Nascimento M.V.M., Florentino I.F. et al. The anxiolytic-like effect of an essential oil derived from *Spiranthera odoratissima* A. St. Hil. leaves and its major component, β -caryophyllene, in male mice. *Prog. Neuropsychopharmacol. Biol. Psychiatry* (2012) **38** 276–284.
 - 54 Oyemitan I.A., Elusiyan C.A., Akanmu M.A., Olugbade T.A. Hypnotic, anticonvulsant and anxiolytic effects of 1-nitro-2-phenylethane isolated from the essential oil of *Dennettia tripetala* in mice. *Phytomedicine* (2013) **20** 1315–1322.
 - 55 Shri R., Bhutani K.K., Sharma A. A new anxiolytic fatty acid from *Aethusa cynapium*. *Fitoterapia* (2010) **81** 1053–1057.
 - 56 Kumar D., Bhat Z.A. Apigenin 7-glucoside from *Stachys tibetica* Vatke and its anxiolytic effect in rats. *Phytomedicine* (2014) **21** 1010–1014.
 - 57 ANVISA – Agência Nacional de Vigilância Sanitária. [Online] 2014. <http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Inicio/Medicamentos/Assunto+de+Interesse/Medicamentos+fitoterapicos> (accessed 20 August 2014).
 - 58 EMA – European Medicines Agency. Herbal medicines for human use. [On line] 2015. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000208.jsp&mid=WC0b01ac05800240cf (accessed 02 February 2015).
 - 59 EMA - European Medicines Agency. Herbal medicines for human use. [On line] 2015. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fherbal_search.jsp&mid=WC0b01ac058001fa1d&searchkwByEnter=false&alreadyLoaded=true&isNewQuery=true&keyword=Enter+keywords&searchType=Latin+name+of+the+genus&taxonomyPath=&treeNumber (accessed 02 February 2015).
 - 60 Ehrenschaft M., Roberts J.E., Mason R.P. Hypericin-mediated photooxidative damage of α -crystallin in human lens epithelial cells. *Free Radic. Biol. Med.* (2013) **60** 347–354.
 - 61 Klemow K.M., Bartlow A., Crawford J., Kocher N., Shah J., Ritsick M. Medical attributes of St. John's Wort (*Hypericum perforatum*), in: Benzie I.F.F., Sissi W.G. (Eds), *Herbal medicine: biomolecular and clinical aspects*, 2nd edn, CRC Press/Taylor & Francis, Boca Raton (FL), pp. 1–27.

- 62 Kaehler S.T., Sinner C., Chatterjee S.S., Philippu A. Hyperforin enhances the extracellular concentrations of catecholamines, serotonin and glutamate in the rat locus coeruleus. *Neurosci. Lett.* (1999) **262** 199–202.
- 63 Vance K.M., Ribnick D.M., Hermann G.E., Rogers R.C. St. John's Wort enhances the synaptic activity of the nucleus of the solitary tract. *Nutrition* (2014) **30** 37–42.
- 64 Leuner K., Kazanski V., Müller M. et al. Hyperforin – a key constituent of St. John's wort specifically activates TRPC6 channels. *FASEB J.* (2007) **21** 4101–4111.
- 65 Singer A., Wonnemann M., Müller W.E. Hyperforin, a major antidepressant constituent of St. John's wort, inhibits serotonin uptake by elevating free intracellular Na⁺. *J. Pharmacol. Exp. Ther.* (1999) **290** 1363–1368.
- 66 Grobler A.C., Matthews G., Molenberghs G. The impact of missing data on clinical trials: a re-analysis of a placebo controlled trial of *Hypericum perforatum* (St John's wort) and sertraline in major depressive disorder. *Psychopharmacology* (2014) **231** 1987–1999.
- 67 Sarris J., Fava M., Schweitzer I., Mischoulon D. St John's Wort (*Hypericum perforatum*) versus sertraline and placebo in major depressive disorder: continuation data from a 26-week RCT. *Pharmacopsychiatry* (2012) **45** 275–278.
- 68 Linde K., Ramirez G., Mulrow C.D., Pauls A., Weidenhammer W., Melchart D. St John's wort for depression an overview and meta-analysis of randomised clinical trials. *BMJ* (1996) **313** 253–258.
- 69 Linde K., Knüppel L. Large-scale observational studies of hypericum extracts in patients with depressive disorders – a systematic review. *Phytomedicine* (2005) **12** 148–157.
- 70 Miroddi M., Calapai G., Navarra M., Minciullo P.L., Gangemi S. *Passiflora incarnata* L.: ethnopharmacology, clinical application, safety and evaluation of clinical trials. *J. Ethnopharmacol.* (2013) **150** 791–804.
- 71 Nascimento D.F., Santana A.P.M., Leite I.O. et al. Clinical toxicology study of an herbal medicine with *Passiflora incarnata* L., *Crataegus oxyacantha* L., *Salix alba* L. in healthy volunteers. *Rev. Bras. Farmacogn.* (2009) **19** 261–268.
- 72 Marchart E., Krenn L., Kopp B. Quantification of the flavonoid glycosides in *Passiflora incarnata* by capillary electrophoresis. *Planta Med.* (2003) **69** 452–466.
- 73 Sundaraganesan N., Mariappan G., Manoharan S. Molecular structure and vibrational spectroscopic studies of Chrysin using HF and Density Functional Theory. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* (2012) **87** 67–76.
- 74 Zanolli P., Avallone R., Baraldi M. Behavioral characterization of the flavonoids apigenin and Chrysin. *Fitoterapia* (2000) **71** 117–123.
- 75 Brown E., Hurd N.S., McCall S., Ceremuga T.E. Evaluation of the anxiolytic effects of chrysin, a *Passiflora incarnata* extract, in the laboratory rat. *AANA J.* (2007) **75** 333–337.
- 76 Wolfman C., Viola H., Paladini A., Dajas F., Medina J.H. Possible anxiolytic effects of chrysin, a central benzodiazepine receptor ligand isolated from *Passiflora coerulea*. *Pharmacol. Biochem. Behav.* (1994) **47** 1–4.
- 77 Singh Y.N., Singh N.N. Therapeutic potential of kava in the treatment of anxiety disorders. *CNS Drugs* (2002) **16** 731–743.
- 78 Sarris J., Kean J., Schweitzer J., Lake J.H. Complementary medicines (herbal and nutritional products) in the treatment of Attention Deficit Hyperactivity Disorder (ADHD): a systematic review of the evidence. *Complement. Ther. Med.* (2011) **19** 216–227.
- 79 Teschke R., Lebot V. Proposal for a kava quality standardization code. *Food Chem. Toxicol.* (2011) **49** 2503–2516.
- 80 Tzeng Y.M., Lee M.J. Neuroprotective properties of kavalactones. *Neural Regen. Res.* (2015) **10** 875–877.
- 81 Schirmacher K., Busselberg D., Langosch J.M., Walden J., Winter U., Bingmann D. Effects of (±)-kavain on voltage-activated inward currents of dorsal rhizome ganglion cells from neonatal rats. *Eur. Neuropsychopharmacol.* (1999) **9** 171–176.
- 82 Uebelhack R., Franke L., Schewe H.J. Inhibition of platelet MAO-B by kava pyrone-enriched extract from *Piper methysticum* Foster (kava-kava). *Pharmacopsychiatry* (1998) **31** 187–192.
- 83 Seitz U., Schulle A., Gleitz J. [3H]-monoamine uptake inhibition properties of kava pyrones. *Planta Med.* (1997) **63** 548–549.
- 84 Wu D., Yu L., Nair M.G., DeWitt D.L., Ramsewak R.S. Cyclooxygenase enzyme inhibitory compounds with antioxidant activities from *Piper methysticum* (kava-kava) roots. *Phytomedicine* (2002) **9** 41–47.
- 85 Lehmann E., Kinzler E., Friedemann J. Efficacy of a special Kava extract (*Piper methysticum*) in patients with states of anxiety, tension and excitedness of non-mental origin – a double-blind placebo-controlled study of four weeks treatment. *Phytomedicine* (1996) **3** 113–119.
- 86 Sarris J., Stough C., Bousman C.A. et al. Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. *J. Clin. Psychopharmacol.* (2013) **33** 643–648.
- 87 Ketola R.A., Viinamäki J., Rasanen I., Pelander A., Goebeler S. Fatal kavalactones intoxication by suicidal intravenous injection. *Forensic Sci. Int.* (2015) **249** 7–11.
- 88 Pinheiro M.L.P., Alcântara C.E.P., Moraes M., Andrade E.D. *Valeriana officinalis* L. for conscious sedation of patients submitted to impacted lower third molar surgery: a randomized, double-blind, placebo-controlled split-mouth study. *J. Pharm. Bioallied.* (2014) **6** 109–114.
- 89 Kennedy D.O., Little W., Haskell C.F., Scholey A.B. Anxiolytic effects of a combination of *Melissa officinalis* and *Valeriana officinalis* during laboratory induced stress. *Phytother. Res.* (2006) **20** 96–102.
- 90 Schmitz M., Jäckel M. Comparative study for assessing quality of life of patients with exogenous sleep disorders (temporary sleep onset and sleep interruption disorders) treated with a hops-valerian preparation and a benzodiazepine drug. *Wien. Med. Wochenschr.* (1998) **148** 291–298.

- 91 WHO – World Health Organization. Monographs on selected medicinal plants (1999) 1 267–276.
- 92 European Pharmacopoeia. Valerian root, 3rd edn. Council of Europe Dep for the Quality of Medicines, Strasbourg, 1998.
- 93 American Herbal Pharmacopoeia. Valerian root. *Valeriana officinalis*. Analytical, quality control and therapeutic monograph, in: Roy Upton. (Ed.), American herbal pharmacopoeia and therapeutic compendium, CSS Associates, USA, 1999, pp. 13–18.
- 94 EMA - European Medicines Agency. Herbal medicines for human use. Community Herbal Monograph on *Valeriana officinalis* L., Radix, 2006.
- 95 Houghton P.J. The scientific basis for the reputed activity of valerian. J. Pharm. Pharmacol. (1999) 51 505–512.
- 96 Kennedy D.O., Wightman E.L. Herbal extracts and phytochemicals: plant secondary metabolites and the enhancement of human brain function. Adv. Nutr. (2011) 2 32–50.
- 97 Benke D., Barberies A., Kopp S. et al. GABA_A receptors as in vivo substrate for the anxiolytic action of valerenic acid, a major constituent of valerian root extracts. Neuropharmacology (2009) 56 174–181.
- 98 Becker A., Felgentreff F., Schröder H., Meier B., Brattström A. The anxiolytic effects of a Valerian extract is based on Valerenic acid. BMC Complement. Altern. Med. (2014) 14 1–5.
- 99 Gharib M., Samani L.N., Panah Z.E., Naseri M., Bahrani N., Kiani K. The effect of valeric on anxiety severity in women undergoing hysterosalpingography. Glob. J. Health. Sci. (2015) 7 358–363.
- 100 Andreatini R., Sartori V.A., Seabra M.L., Leite J.R. Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. Phytother. Res. (2002) 16 650–654.
- 101 American Herbal Pharmacopoeia Botanical Pharmacognosy. *Actea racemosa* L. syn. *Cimicifuga racemosa* (L.) Nutt, in: Roy Upton. (Ed.) American herbal pharmacopoeia botanical pharmacognosy, CRC Press, USA, 2011, pp. 217–222.
- 102 Pengelly A., Bennet K. Appalachian plant monographs. Black cohosh *Actea racemosa* L., 2012. <http://www.frostburg.edu/aces/appalachian-plants/>.
- 103 European Medicines Agency (EMA). Assessment report on *Cimicifuga racemosa* (L.) Nutt., rhizome, EMA, United Kingdom, 2008.
- 104 Bolle P., Mastrangelo S., Perrone F., Evandri M.G. Estrogen-like effect of a *Cimicifuga racemosa* extract sub-fraction as assessed by *in vivo*, *ex vivo* and *in vitro* assays. J. Steroid Biochem. Mol. Biol. (2007) 107 262–269.
- 105 Mohammad-Alizadeh-Charandabi S., Shahnazi M., Nahae J., Bayatipayan S. Efficacy of black cohosh (*Cimicifuga racemosa* L.) in treating early symptoms of menopause: a randomized clinical trial. Chin. Med. (2013) 8 1–7.
- 106 Nikolić D., Li J., Van Breemen R.B. Metabolism of N-methylserotonin, a serotonergic constituent of black cohosh (*Cimicifuga racemosa*, L. (Nutt.)), by human liver microsomes. Biomed. Chromatogr. (2014) 28 1647–1651.
- 107 Amsterdam J.D., Yao Y., Mao J.J. Randomized, double-blind, placebo-controlled trial of *Cimicifuga racemosa* (black cohosh) in women with anxiety disorder due to menopause. J. Clin. Psychopharmacol. (2009) 29 478–483.
- 108 Paula J.A.M., Paula J.R., Bara M.T.F., Rezende M.H., Ferreira H.D. Estudo farmacognóstico das folhas de *Pimenta pseudocaryophyllus* (Gomes) L.R. Landrum – Myrtaceae. Rev. Bras. Farmacogn. (2008) 18 265–278.
- 109 Paula J.A.M., Ferri P.H., Bara M.T.F., Tresvenzol L.M.F., Sá F.A.S., Paula J.R. Intraspecific chemical variability in the essential oils of *Pimenta pseudocaryophyllus* (Gomes) L.R. Landrum (Myrtaceae). Biochem. System. Ecol. (2011) 39 643–650.
- 110 Landrum L.R. Flora neotropica: monograph 45 Campomanesia, Pimenta, Blepharocalyx, Legrandia, Acca, Myrrhinium, and Luma (Myrtaceae). Organization for Flora Neotropica, New York, 1985.
- 111 Nakaoka-Sakita M., Aguiar O.T., Yatagai M., Igarashi T. Óleo essencial de *Pimenta pseudocaryophyllus* var. *pseudocaryophyllus* (Gomes) Landrum (Myrtaceae) I: cromatografia a gás/espectrometria de massa (GC/EM). Rev. Inst. Flor. (1994) 6 53–61.
- 112 Landrum L.R., Kawasaki M.L. The genera of Myrtaceae in Brazil: an illustrated synoptic treatment and identification keys. Brittonia (1997) 49 508–536.
- 113 Lima M.E.L., Cordeiro I., Young M.C.M., Sobra M.E.G., Moreno P.R.H. Antimicrobial activity of the essential oil from two specimens of *Pimenta pseudocaryophyllus* (Gomes) L.R. Landrum (Myrtaceae) native from São Paulo State – Brazil. Pharmacologyonline (2006) 3 589–593.
- 114 Santos B.C.B., Silva J.C.T., Guerrero Júnior P.G., Leitão G.G., Barata L.E.S., Isolation of chavibetol from essential oil of *Pimenta pseudocaryophyllus* leaf by high-speed counter-current chromatography. J. Chromatogr. (2009) 1216 4303–4306.
- 115 Fajemiroye J.O., Polepally P.R., Chaurasiya N.D., Tekwani B.L., Zjawiony J.K., Costa E.A. Oleanolic acid acrylate elicits antidepressant-like effect mediated by 5-HT_{1A} receptor. Sci. Rep. (2015) 5 11582.
- 116 Fajemiroye J.O., Martins J.L.R., Brito A.F. et al. Central activities of *Pimenta pseudocaryophyllus* (Gomes) L.R. Landrum. IJMAP (2012) 2 118–122.
- 117 Paula J.A.M., Silva M.R.R., Costa M.P. et al., Phytochemical analysis and antimicrobial, antinociceptive, and anti-inflammatory activities of two chemotypes of *Pimenta pseudocaryophyllus* (Myrtaceae). J. Evid. Based. Complement. Altern. Med. (2012) 2012 Article ID 420715, 15 pages.
- 118 Sporn M.B., Honda T., Finlay H.J., Gribble G.W., Suh N., Michael B. New enone derivatives of oleanolic acid and ursolic acid as inhibitors of nitric oxide production in mouse macrophages. Bioorg. Med. Chem. Lett. (1997) 7 1623–1628.
- 119 Sporn M.B., Honda T., Rounds B.V., Gribble G.W., Suh N., Wang Y. Design and synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages. Bioorg. Med. Chem. Lett. (1998) 8 2711–2714.

- 120 Sevik H., Guney K. Effects of IAA, IBA, NAA, and GA3 on rooting and morphological features of *Melissa officinalis* L. stem cuttings. *ScientificWorldJournal* (2013) **2013** Article ID 909507, 5 pages.
- 121 Emamghoreishi M., Talebianpour M.S. Antidepressant effect of *Melissa officinalis* in the forced swimming test. *DARU* (2009) **17** 42–47.
- 122 Obulesu M., Rao D.M. Effect of plant extracts on Alzheimer's disease: an insight into therapeutic avenues. *J. Neurosci. Rural Pract.* (2011) **2** 56–61.
- 123 Taiwo A.E., Leite F.B., Lucena G.M. et al. Anxiolytic and antidepressant-like effects of *Melissa officinalis* (lemon balm) extract in rats: influence of administration and gender. *Indian J. Pharmacol.* (2012) **44** 189–192.
- 124 Kennedy D.O., Scholey A.B., Tildesley N.T., Perry E.K., Wesnes K.A. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). *Pharmacol. Biochem. Behav.* (2002) **72** 953–964.
- 125 Kennedy D.O., Savelev G.S., Tildesley N.T.J., Perry E.K., Wesnes K.A., Schole Y.A.B. Modulation of mood and cognitive performance following acute administration of single doses of *Melissa officinalis* (Lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties. *Neuropsychopharmacology* (2003) **28** 1871–1881.
- 126 Guginskia G., Luiz A.P., Silva M.D. et al. Mechanisms involved in the antinociception caused by ethanolic extract obtained from the leaves of *Melissa officinalis* (lemon balm) in mice. *Pharmacol. Biochem. Behav.* (2009) **93** 10–16.
- 127 Alijaniha F., Naseri M., Afsharypour S. et al. Heart palpitation relief with *Melissa officinalis* leaf extract: double blind, randomized, placebo controlled trial of efficacy and safety. *J. Ethnopharmacol.* (2015) **164** 378–384.
- 128 Awad R., Muhammad A., Durst T., Trudeau V.L., Arnason J.T. Bioassay-guided fractionation of lemon balm (*Melissa officinalis* L.) using an *in vitro* measure of GABA transaminase activity. *Phytother. Res.* (2009) **23** 1075–1081.
- 129 Akhondzadeh S., Noroozian M., Mohammadi M., Ohadinia S., Jamshidi A.H., Khani M. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. *J. Neurol. Neurosurg. Psychiatry* (2003) **74** 863–866.
- 130 Dog L.T., Powell L.K., Weisman M.S. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. *Menopause J.* (2003) **10** 299–313.
- 131 McKenna D.J., Jones K., Humphrey S., Hughes K. Black cohosh: efficacy, safety, and use in clinical and preclinical applications. *Altern. Ther. Health Med.* (2001) **7** 93–100.
- 132 Netfarma. Bula de medicamento. Available at: <http://www.netfarma.com.br/geraBula.asp?NomeArquivoBula=P00002MRJ00.pdf> (accessed 10 August 2015).
- 133 Silva A.G., Brandão A.B., Cacciari R.S., Soares W.H. Avanços na elucidação dos mecanismos de ação de *Cimicifuga racemosa* (L.) Nutt. nos sintomas do climatério. *Rev. Bras. Pl. Med.* (2009) **11** 455–464.
- 134 Guzmán-Gutiérrez S.L., Bonilla-Jaime H., Gómez-Cansino R., Reyes-Chilp R. Linalool and β -pinene exert their antidepressant-like activity through the monoaminergic pathway. *Life Sci.* (2015) **128** 24–29.
- 135 Guzman-Gutiérrez S.L., Gomez-Cansino R., Garcia-Zebadua J.C., Jimenez-Perez N.C., Reyes-Chilpa R. Antidepressant activity of *Litsea glaucescens* essential oil: identification of beta-pinene and linalool as active principles. *J. Ethnopharmacol.* (2012) **143** 673–679.
- 136 Bilia A.R., Gallori S., Vincieri F.F. St. John's wort and depression efficacy, safety and tolerability-an update. *Life Sci.* (2002) **70** 3077–3096.
- 137 Russo E., Scicchitano F., Whalley B.J. et al. Hypericum perforatum: pharmacokinetic, mechanism of action, tolerability, and clinical drug-drug interactions. *Phytother. Res.* (2013) **28** 643–655.
- 138 Chu C.J., Kemper K.J. Lavender (*Lavandula* spp.). Longwood Herbal Task Force, (2001) 1–31.: <http://www.mcp.edu/herbal/>
- 139 Akhondzadeh S., Kashani L., Fotouhi A. et al. Comparison of *Lavandula angustifolia* Mill. tincture and imipramine in the treatment of mild to moderate depression: a double-blind, randomized trial. *Prog. Neuropsychopharmacol. Biol. Psychiatry* (2003) **27** 123–127.
- 140 Chioca L.R., Ferro M.M., Baretta I.P. et al. Anxiolytic-like effect of lavender essential oil inhalation in mice: participation of serotonergic but not GABA_A/benzodiazepine neurotransmission. *J. Ethnopharmacol.* (2013) **147** 412–418.
- 141 Sporn M.B., Honda T., Honda Y. et al. A novel dicyanotriterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile, active at picomolar concentrations for inhibition of nitric oxide production. *Bioorg. Med. Chem. Lett.* (2002) **12** 1027–1030.
- 142 Sporn M.B., Liby K.T., Yore M.M., Fu L., Lopchuk J.M., Gribble G.W. New synthetic triterpenoids: potent agents for prevention and treatment of tissue injury caused by inflammatory and oxidative stress. *J. Nat. Prod.* (2011) **74** 537–545.
- 143 Sriram N.G.S., Kavitha V.M.J., Sasikumar S.C., Rajeswari R. Phytochemical screening and antimicrobial activity of the plant extracts of *Mimosa pudica* L. against selected microbes. *Ethnobot. Leaflet.* (2009) **13** 618–624.
- 144 Guzmán-Gutiérrez S.L., Reyes-Chilpa R., Bonilla-Jaime H. Medicinal plants for the treatment of “nervios”, anxiety, and depression in Mexican Traditional Medicine. *Rev. Bras. Farmacogn.* (2014) **24** 591–608.
- 145 Zaware B.B., Chaudhari S.R., Shinde M.T. An overview of *Mimosa pudica* Linn.: chemistry and pharmacological profile RJPBCS. (2014) **5** 754–761.
- 146 Escribano P., Viruel M.A., Hormaza J.I. Characterization and cross-species amplification of microsatellite markers in cherimoya (*Annona cherimola* Mill., Annonaceae). *Mol. Ecol. Notes* (2004) **4** 746–748.
- 147 Martínez-Vázquez M., Estrada-Reyes R., Escalona A.G.A. et al. Antidepressant-like effects of an alkaloid extract of the

- aerial parts of *Ammonia chermolia* in mice. *J. Ethnopharmacol.* (2012) **139** 164–170.
- 148 Bonilla-Jaime H., Guadarrama-Cruz G., Alarcon-Aguilar F.J., Limón-Morales O., Vazquez-Palacios G. Antidepressant-like activity of *Tagetes lucida* Cav. is mediated by 5-HT_{1A} and 5-HT_{2A} receptors. *J. Nat. Med.* (2015) **4** 463–467.
 - 149 Guadarrama-Cruz G., Alarcón-Aguilar F.J., Vega-Avila E., Vázquez-Palacios G., Bonilla-Jaime H. Antidepressant-like effect of *Tagetes lucida* Cav. extract in rats: involvement of the serotonergic system. *AJCM's* (2012) **40** 753–768.
 - 150 Estrada-Reyes R., López-Rubalcava C., Ferreyra-Cruz O.C. et al. Central nervous system effects and chemical composition of two subspecies of *Agastache mexicana*; an ethnomedicine of Mexico. *J. Ethnopharmacol.* (2014) **153** 98–110.
 - 151 González-Trujano M.E., Ponce-Muñoz H., Hidalgo-Figueroa S., Navarrete-Vázquez G., Estrada-Soto S. Depressant effects of *Agastache mexicana* methanol extract and one of major metabolites tilianin. *APJTB* (2015) **8** 185–190.
 - 152 Galvez J., Estrada-Reyes R., Benítez-King G. et al. Involvement of the GABAergic system in the neuroprotective and sedative effects of 7-O-glucoside in rodents. *Restor. Neurol. Neurosci.* (2015) **33** 1–18.
 - 153 Fahami F., Asali Z., Aslani A., Fathizadeh N. A comparative study on the effects of *Hypericum perforatum* and passion flower on the menopausal symptoms of women referring to Isfahan city health care centers. *J. Nurs. Midwifery Res.* (2010) **15** 202.
 - 154 Patočka J., Jakl J. Biomedically relevant chemical constituents of *Valeriana officinalis*. *J. Appl. Biomed.* (2010) **8** 11–18.
 - 155 Bourin M., Petit-Demoulière B., Dhonnchadha B.N., Hascoet M. Animal models of anxiety in mice. *Fundam. Clin. Pharmacol.* (2007) **21** 567–574.
 - 156 Crawley J.N., Goodwin F.K. Preliminary report of a simple animal behavior for the anxiolytic effects of benzodiazepines. *Pharmacol. Biochem. Behav.* (1980) **13** 167–170.
 - 157 File S.E. The use of social interaction as a method for detecting anxiolytic activity of chlordiazepoxide-like drugs. *J. Neurosci. Methods* (1980) **2** 219–238.
 - 158 Hall C.S. Emotional behavior in the rat. I. Defecation and urination as measures of individual differences in emotionality. *J. Comp. Psychol.* (1934) **18** 385–403.
 - 159 Prut L., Belzung C. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. *Eur. J. Pharmacol.* (2003) **463** 3–33.
 - 160 Archer J. Tests for emotionality in rats and mice: a review. *Anim. Behav.* (1973) **21** 205–235.
 - 161 Bourin M., Hascoët M. The mouse light/dark box test. *Eur. J. Pharmacol.* (2003) **463** 55–65.
 - 162 Crawley J.N. Exploratory behavior models of anxiety in mice. *Neurosci. Biobehav. Rev.* (1985) **9** 37–44.
 - 163 Pellow S., Chopin P., Briley M., Briley M. The validation of open: closed arm entries in an elevated plus-maze: a novel test of anxiety in the rat. *J. Neurosci. Methods* (1985) **14** 149–167.
 - 164 Rodgers R.J., Dalvi A. Anxiety, defense and the elevated plus-maze. *Neurosci. Behav.* (1997) **21** 801–810.
 - 165 Crawley J.N. What's wrong with my mouse?, in: Jacqueline N. Crawley. (Ed.) Behavioral phenotyping of transgenic and knockout mice, 2nd edn, John Wiley & Sons, New York, 2007, pp. 100–150.
 - 166 Crawley J.N. Behavioral phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioral tests. *Brain Res.* (1999) **835** 18–26.
 - 167 Nardo M., Casarotto P.C., Gomes F.V., Gumariães F.S. Cannabidiol reverses the mCPP-induced increase in marble-burying behavior. *Fundam. Clin. Pharmacol.* (2014) **28** 544–550.
 - 168 Porsolt R.D., Le Pichon M., Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature* (1977) **266** 730–732.
 - 169 Slattery D.A., Cryan J.F. Using the rat forced swim test to assess antidepressant-like activity in rodents. *Nat. Protoc.* (2012) **7** 1009–1014.
 - 170 Steru L., Chermat R., Thierry B., Simon P. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology* (1985) **85** 367–370.
 - 171 Cryan J.F., Mombereau C., Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. *Neurosci. Biobehav.* (2005) **29** 571–625.
 - 172 Takahashi M., Satou T., Ohashi M., Hayashi S., Sadamoto K., Koike K. Interspecies comparison of chemical composition and anxiolytic-like effects of lavender oils upon inhalation. *NPC* (2011) **6** 1769–1774.
 - 173 Woronuk G., Demissie Z., Rheault M., Mahmoud S. Biosynthesis and therapeutic properties of *Lavandula* essential oil constituents. *Planta Med.* (2011) **77** 7–15.