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Review

Therapeutical strategies for anxiety and anxiety-like disorders using plant-derived natural compounds and plant extracts

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ABSTRACT

Anxiety and anxiety-like disorders describe many mental disorders, yet fear is a common overwhelming symptom often leading to depression. Currently two basic strategies are discussed to treat anxiety: pharmacotherapy or psychotherapy. In the pharmacotherapeutical clinical approach, several conventional synthetic anxiolytic drugs are being used with several adverse effects. Therefore, studies to find suitable safe medicines from natural sources are being sought by researchers. The results of a plethora experimental studies demonstrated that dietary phytochemicals like alkaloids, terpenes, flavonoids, phenolic acids, lignans, cinnamates, and saponins or various plant extracts with the mixture of different phytochemicals possess anxiolytic effects in a wide range of animal models of anxiety. The involved mechanisms of anxiolytics action include interaction with γ-aminobutyric acid A receptors at benzodiazepine (BZD) and non-BZD sites with various affinity to different subunits, serotonergic 5-hydrodytryptamine receptors, noradrenergic and dopaminergic systems, glutamate receptors, and cannabinoid receptors. This review focuses on the use of both plant-derived natural compounds and plant extracts with anxiolytic effects, describing their biological effects and clinical application.

1. Introduction

Anxiety and related disorders are among the most common of mental disorders. The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) principles arranged the anxiety disorder spectrum into separate groups for the classical anxiety disorders, trauma- and stressor-related disorders, obsessive-compulsive and related disorders, and dissociative disorders. Based on DSM-5, the classical anxiety disorders also include selective mutism and separation anxiety disorder [1]. According to large population-based surveys, up to 33.7% of the population are affected by an anxiety disorder during their lifetime; it has higher prevalence than the lifetime prevalence of mood disorders and substance use disorders [2–6]. A broad range of mental declines are included in the definition of anxiety or anxiety-like disorders. They are

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commonly diagnosed using mental questionnaires and by oral interactions with patient. Instrumental tools like magnetic resonance are used to map the focal point of the disease [7]. Neither diagnosis nor therapy is easy, as the sub-conscious and conscious are involved. Understanding the pathophysiology is crucial for accurate diagnosis [8]. Generally, anxiety is a normal human emotion which arises during stress and/or discomfort. However, when left uncontrolled, anxiety can lead to debilitating overwhelming fear. Patients are mentally crippled, expressing a wide variety of symptoms including restlessness, worry, irritability, muscle tension and sleep problems.

Many symptoms are similar to those which occur in depression and anxiety could ultimately lead to depression [9,10]. But, compared to depression, anxiety disorders are rarely self-diagnosed while depression is often recognized by patients. Recently Coles and co-workers reported that 50% of patients recognized depression while only 20% correctly recognized anxiety [11]. The findings of Sun et al. [12] suggest that anxiety, depression, and helplessness are important correlates of obsessive-compulsive disorders in Chinese adolescents and it is evident that these different mental disorders have several common signs. More than half of patients with an anxiety disorder have multiple anxiety disorders [2,13], and almost 30% will have three or more comorbid anxiety or related disorders [2]. Anxiety is often associated with substance use and mood disorders [2,14]. An estimated 52% of patients with bipolar disorder [15], 60% of patients with major depressive disorder [16], and 47% of those with attention deficit hyperactivity disorder [17] will have an anxiety or related a comorbidity. The high frequency of comorbidity must be considered when diagnosing anxiety and related disorders since this can have important implications for diagnosis and treatment [18]. Anxiety disorders associated with other anxiety or depressive disorders are associated with poorer treatment outcomes and greater severity [19–22], increased functional impairment [20], increased health service use [23], and higher treatment costs [24]. Patients with anxiety disorders have a higher prevalence of hypertension and other cardiovascular conditions, gastrointestinal disease, arthritis, thyroid disease, respiratory disease, migraine headaches, and allergic conditions compared to those without anxiety disorders [25]. Anxiety has a considerable economic impact on society as well, being associated with greater use of health care services [4,26] and decreased work productivity [26,27]. Importantly, studies report that about 40% of patients diagnosed with anxiety and related disorder remain untreated [4,28].

The manifestation of anxiety and anxiety-like disorders involves a coordinated activity of numerous brain signalling pathways involving different neurotransmitters. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter which is known to counterbalance the action of the excitatory neurotransmitter glutamate. Other neurotransmitters that modulate complex anxiety responses in the amygdala, including serotonin, opioid peptides, endocannabinoids, neuropeptide Y, oxytocin, and corticotrophin-releasing hormone [29]. GABAergic inhibition is essential for maintaining a balance between neuronal excitation and inhibition in the central nervous system (CNS) [29]. Neuronal inhibition by GABA is mediated by two distinct classes of GABA receptors. Ionotropic $GABA_A$ receptor is fast-acting ligand-gated chloride channel responsible for rapid inhibition [30]. $GABA_B$ receptor is coupled indirectly via G-proteins to either calcium or potassium channels to produce slow and prolonged inhibitory responses which is involved in the processes of myorelaxation [31]. The $GABA_A$ receptor is a transmembrane hetero-oligomer with pentameric structure (α_1, α_2, β_1, β_2, and γ subunits) located in the neuronal membrane as is showed in Fig. 1. Activation of $GABA_A$ receptors causes an immediate and substantial rise in chloride conductance across the cell membrane, which renders the neuron unable to raise an action potential and leads to “phasic” inhibition of the neuron [32,33]. Preclinical studies demonstrated that the α_2 subunit of $GABA_A$ receptor is particularly relevant for the manifestation of anxiety [34]. The neural circuits involved in anxiety comprise inhibitory networks of principally GABAergic interneurons. It is supposed that the presence of allosteric sites on the GABAA receptor allows the level of inhibition of the neuron to be regulated with exquisite precision using different classes of anxiolytic and sedative–hypnotic drugs such as benzodiazepines, barbiturates, or neurosteroids. However, these allosteric sites can be modulated also by wide spectrum of plant natural compounds. Consequent changes in the subunit composition and conformation of the $GABA_A$ receptor may represent mechanisms whereby the level of neuronal activity may be affected in pathological anxiety states [29].

1.1. Pharmacotherapy of anxiety using synthetic drugs

Anxiety can be controlled by pharmacotherapy and/or psychotherapy. Antianxiety agents (anxiolytics) are used in pharmacotherapy [35–37]. The commonly recommended pharmacological agents for treatment of different anxiety and related disorders are benzodiazepines (BDZ), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and reversible inhibitors of monoamine oxidase A (RIMAs). BDZ are the first-line pharmacological anxiolytics drugs, and advanced psychoactive medications were developed in the last 45 years. However, their long-term use is impaired by tolerance development and abuse liability [38–40]. BDZ may be useful as adjunctive therapy early in treatment, particularly for acute anxiety or agitation, to help patients in times of acute crises, or while waiting for onset of adequate efficacy of SSRIs or other antidepressants [18]. Recent clinical outcomes have shown that SSRIs are effective on various anxiety disorders but have a slow onset of action [41–45]. SSRIs and SNRIs are usually preferred as initial treatments, since they are generally safer and better tolerated than TCAs or MAOIs [18]. Several anticonvulsants and atypical antipsychotics have demonstrated efficacy in some anxiety and related disorders, but for various reasons, including side effects, as well as limited trial data and clinical experience, these agents are generally recommended as adjunctive therapies. The choice of medication should take into consideration the evidence for its efficacy and safety/tolerability for the treatment of the specific anxiety and related disorder, as well as for any comorbid conditions the patient might have, in both acute and long-term use [18]. Although benzodiazepines, SSRIs, SNRIs and other anxiolytics are often effective, it is clear there is a need for rapidly acting, better tolerated medications with a greater and more sustained response. In this regard, there are also neurosteroids that are powerful allosteric modulators of $GABA_A$ and glutamate receptors which lack the unwanated side effects of benzodiazepines [46]. Based on findings from a wide range of preclinical and clinical studies, it is proposed that opioid ligands and its receptors are involved in physiological and dysfunctional forms of anxiety [47]. Many neuropeptides are plenteously expressed in specific brain regions which are involved in emotional processing and anxiety behaviours. In this regard, the various neuropeptides represent awaited candidates for new therapeutic ways against anxiety and anxiety-like disorders [48]. Moreover, glutamate-based anxiolytic ligands, which act through decreasing the activity of glutamatergic neurotransmission, may attenuate excitation in the CNS, thus resulting in anxiolysis [49]. Over the last two decades, some of the most promising molecules in pharmacological studies were addressed as prospective substances for development of new anxiolytics. Fig. 2 summarizes the mechanisms of action of prospective molecules with anxiolytic effects, such as Δ^9-tetrahydrocannabinol, modulators of metabotropic glutamate receptors and acid-sensing ion channels, and polyamines that are potentially new substances for the treatment of anxiety [50–58].

1.2. Animal models of anxiety disorders

Animal models are often used for the evaluation of molecular

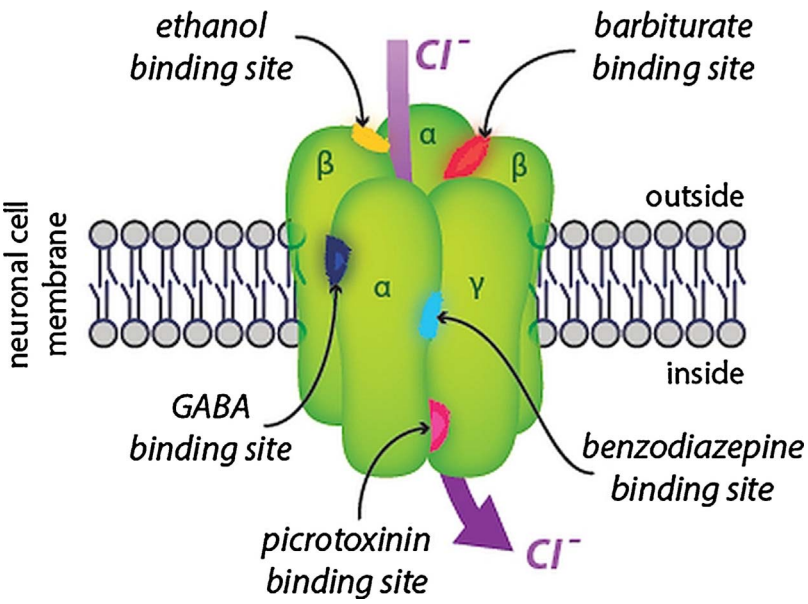

Fig. 1. The pentameric $GABA_A$ ionotropic receptor involved in anxiety by decreasing neuronal excitability.
Fig. shows the receptor binding sites for GABA, benzodiazepines, barbiturates, ethanol, and picrotoxinin on the $GABA_A$ chloride ion channel. Receptor consist of two α subunits, two β subunits, and one γ subunit. The different ligands with sedative (anxiolytic) effects bind to the external binding domain, increasing the conductance of chloride ions through central pore of the receptor, leading to neuronal hyperpolarization. The consequence is an inhibitory effect on the neurotransmission by reducing the stimulation of an action potential.
GABA, gamma-aminobutyric acid.

mechanisms involved in anxiety and for screening and developing novel drugs for new treatment strategies. Animal models of anxiety are based on conflict situations that can generate opposite motivational states induced by approach-avoidance situations. Common animal models of anxiety include the "ethological" tests that evaluate unlearned/unpunished responses (e.g. elevated plus maze, light-dark box, open field, hole-board, forced-swim), on the other hand, models which involve learned/punished responses belong to "conditioned operant conflict tests" (e.g. Vogel conflict test) [59,60].

The elevated plus maze test is based on the natural aversion of mice for open and elevated areas, as well as on their natural spontaneous exploratory behaviour in novel environments. The apparatus consists of open arms and closed arms, crossed in the middle perpendicularly to each other, and a centre area. Mice are given access to all of the arms and are allowed to move freely between them. The number of entries into the open arms and the time spent in the open arms are used as indices of open space-induced anxiety in mice [61]. The light/dark test is based on the innate aversion of rodents to brightly illuminated areas and on the spontaneous exploratory behaviour of rodents in response to mild stressors, that is, novel environment and light. The test apparatus consists of a small dark safe compartment (one third) and a large illuminated aversive compartment (two thirds) [62]. The open field is an arena with walls to prevent escape. The concept is based on conflicting innate tendencies on the avoidance of bright light and open spaces and of exploring novel environments. The result of these two conflictions is anxiety. Similar hole-board test was designed to mitigate the flaws of

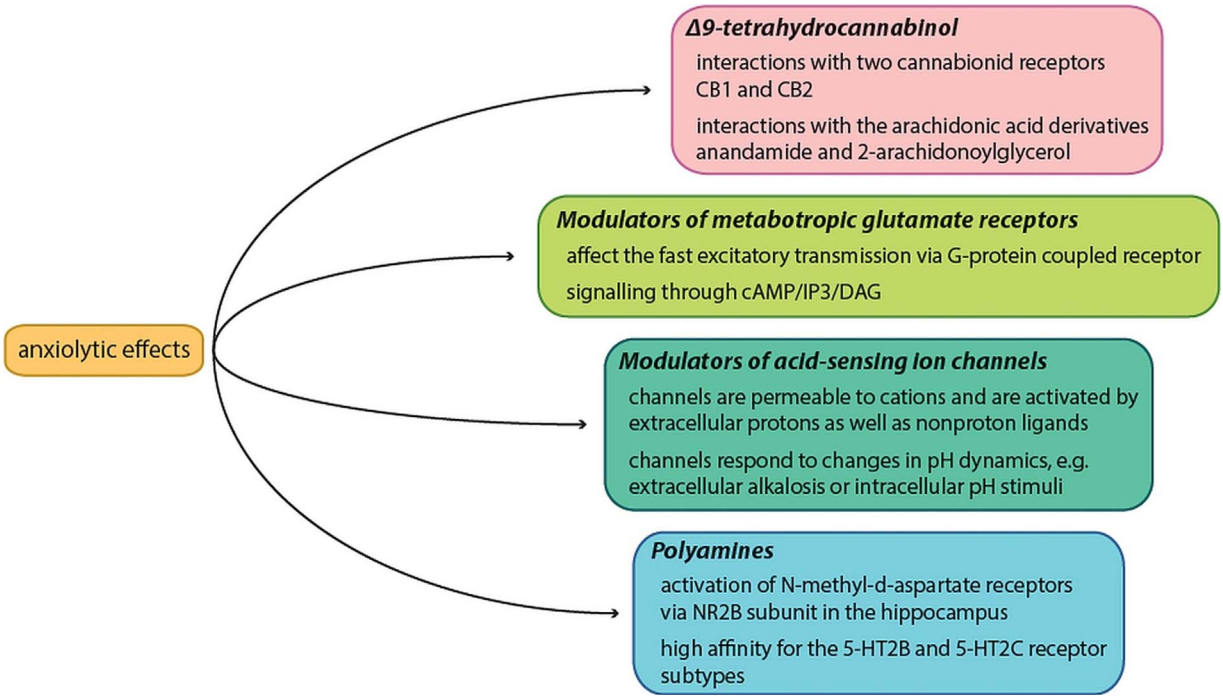

Fig. 2. Perspective molecules with anxiolytic effects: mechanism of action.
Novel molecules with anxiolytic effects include Δ^9-tetrahydrocannabinol, modulators of metabotropic glutamate receptors and acid-sensing ion channels, and polyamines.
cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP3, inositol triphosphate; 5-HT2, 5-hydroxytryptamine receptor 2 also known as serotonin receptor 2B.

the open field test [63]. In another behavioural test, the forced-swim test, rodents are placed in an inescapable transparent tank that is filled with water and their escape related mobility behaviour is measured [64]. A classic protocol of the Vogel conflict test is based on situation where rodents are food or water deprived and then placed in an apparatus while simultaneously exposed to punishment in the shape of a mild shock whenever food or water are retrieved. Anxiety decreases the number of times the animal goes to get food or water. On contrary, anxiolytic drugs increase the number of times animals go up to get food or water, even though the animal will still have been punished [65]. There are many other rodent models to test anxiety disorders, e.g. motor activity, rota-rod, tail suspension, marble-burying, free exploratory, zero-maze, social interaction, supressed feeding latency and isolation-induced aggression.

1.3. Aim of review

It is well-documented that traditional medicine based on plant natural compounds is effective in the treatment of anxiety and anxiety-like disorders in humans [66]. Importantly, long-term administration of plant natural compounds is not linked with clinically serious adverse effects in humans. On the other hand, pharmacotherapeutical clinical approaches demonstrated that using several conventional synthetic anxiolytic drugs is associated with several adverse effects. Therefore, the screening of suitable safe medicines from natural sources is a considerable challenge of ongoing research. Thus, the objectives of this review is to summarize the current knowledge about the anxiolytic effects of both plant-derived natural compounds and plant extracts. Moreover, we will describe the biological effects, cellular signalling pathways, and clinical administration of plant natural substances.

1.4. Source of data

Data from the available biomedical literature were reviewed and pooled to evaluate anti-anxiolytic effects of plant natural compounds or plant extracts. Relevant studies published in the literature were retrieved by the use of terms: anxiety; anxiolytic; anti-anxiety; alkaloids; terpenes; flavonoids; phenolic acid; lignans; cinnamates; saponins; plant extract, as either a keyword or MeSH (medical subject heading) term in searches of the PubMed (US National Library of Medicine National Institutes of Health) bibliographic database. To reduce reporting bias; only preclinical or clinical studies that involved commonly used and generally-known natural compounds were reviewed. We excluded studies that were not primarily aimed at thr evaluation of the anxiolytic effects.

2. Natural compounds

For centuries, plants and plant products were used in medicine. Currently, medicinal plants and their products are used as house remedies. In a 2007 survey by the National Center for Complementary and Alternative Medicine nearly 40% of adults in the United States reported to use complementary and alternative medicine [66].

According to the World Health report, ~450 million people suffer from brain/mental or behavioural disorders, yet only a fraction undergo treatment. While benzodiazepines and other prescription medications are the clinical standard, natural, plant-derived supplements are receiving more attention [67]. Numerous structurally different classes of plant-derived ligands have anxiolytic (-like) properties [67–71], while expressing a high affinity for the benzodiazepine binding site of the A type γ-aminobutyric acid ($GABA_A$) receptor complex [30,32,33]. Fig. 3 shows that different classes of phytochemicals are able to inhibit the excitatory transmission and reduction of anxiety through $GABA_A$-BZD receptor. The comprehensive preclinical research showed that plant-derived chemicals like alkaloids, terpenes, flavonoids, phenolic acids, lignans, cinnamates, and saponins possess anxiolytic effects using various animal models of anxiety.

The alkaloids exhibited promising biological activities and important properties for the treatment of neurodegenerative diseases, including antioxidant, anti-inflammatory effects and also anxiolytic and antidepressant properties. Vogel conflict test in mice was used for the analysis of antianxiety action of diterpene alkaloid songorine. Songorine administered at a dose of 0.25 mg/kg showed significant anxiolytic effects similar with phenazepam and did not produce sedative effect [72]. The anxiolytic-like effects of alkaloid-enriched extract obtained from fresh leaves of the *Argemone mexicana* were analysed in female Wistar rats [73]. Alkaloid-enriched extract at a dose of 0.2 mg/kg manifested anxiolytic-like effects comparable to diazepam 2 mg/kg on elevated plus maze test and did not cause changes in locomotor activity. The usage of picrotoxin impeded the anti-anxiety action of plant alkaloid-enriched extract in animals.

Recent research using rodents indicates that biological activities are also triggered by terpenes, which are synthesized in some medicinal plants [74,75], which affect the central nervous system [76,77]. The diterpene phytol (3,7,11,15-tetrametilhexadec-2-en-1-ol) is a member of branched-chain unsaturated alcohols. Their common characteristics are a single hydroxyl group per molecule and twenty-one double bond carbon atoms ($C_{20}H_{40}O$) resulting in a molecular weight of 296.54 (Fig. 4a). In a motor activity test, phytol (75 mg/kg) impaired the rotarod performance of mice [78], it decreased latency for sleeping (75 mg/kg) and increased the sleep time (25, 50 and 75 mg/kg). The same concentration range also exerts anxiolytic-like effects on mice. Possibly, phytol interacts with $GABA_A$ receptor subtypes that mediate the effects of benzodiazepines [78]. Myrtenol is a monoterpenoid alcohol present in essential oil of *Myrtus communis* L. (Myrtaceae). In animal study, myrtenol demonstrated apparent anxiolytic-like activities using the elevated plus maze, the light-dark transition, the open field and rotarod tests. Moreover, results showed that these effects can be mediated by GABAergic transmission [79]. Another terpene cannabidiol, a phytocannabinoid present in *Cannabis sativa* L., presents anxiolytic- and antipsychotic-like effects in clinical and preclinical studies [80,81]. Single cannabidiol administered at a dose of 3 mg/kg manifested anxiolytic-like effects in non-stressed mice using the elevated plus maze test. The tail suspension test showed that single or repeated cannabidiol lowered the immobility time and this result was similar with imipramine used at a dose of 20 mg/kg. In addition, cannabidiol increased cell proliferation and neurogenesis in the dentate gyrus and subventricular zone [81]. The purpose of another study was to evaluate the anxiolytic and antidepressant activities of asiatic acid, a pentacyclic triterpene from *Centella asiatica* L., and its potential modulation of the $GABA_A$ receptor in male Sprague-Dawley rats. Asiatic acid significantly changed the ratio of open arm time, maximum speed, and time spent mobile. Moreover, flumazenil in combination with asiatic acid suppressed the anxiolytic effects; this result demonstrated that asiatic acid modulates the benzodiazepine site on the $GABA_A$ receptor [82]. The results of Colla et al. [83] revealed that triterpenoid ursolic acid (10 mg/kg) induces an anxiolytic-like effect in mice. The open field test showed the increase in total time in the center and decrease in number of rearing responses, the elevated plus maze found an increase in percentage of entries and total time spent in the open arms. These results with ursolic acid were comparable to diazepam. Another study evaluated anxiolytic properties of monoterpenic phenol carvacrol (5-isopropyl-2-methylphenol), a compound of the essential oil of oregano or thyme [74,84]. Using the male mice model, carvacrol administered orally at a single dose of 12.5, 25 or 50 mg/kg revealed anxiolytic-like effects in the plus maze test. These effects were not affected by the locomotor activity in the open-field test [84].

Ognibene and colleagues [68] evaluated the anxiolytic properties of new halogenated flavonoids, 5-methoxy-6,8-dibromoflavanone and 6-bromoflavanone (Fig. 4b). These two synthetic flavonoids were compared to diazepam (0.5 mg/kg) and the natural compound chrysin (1 mg/kg). Intraperitoneal administration of both flavonoid compounds

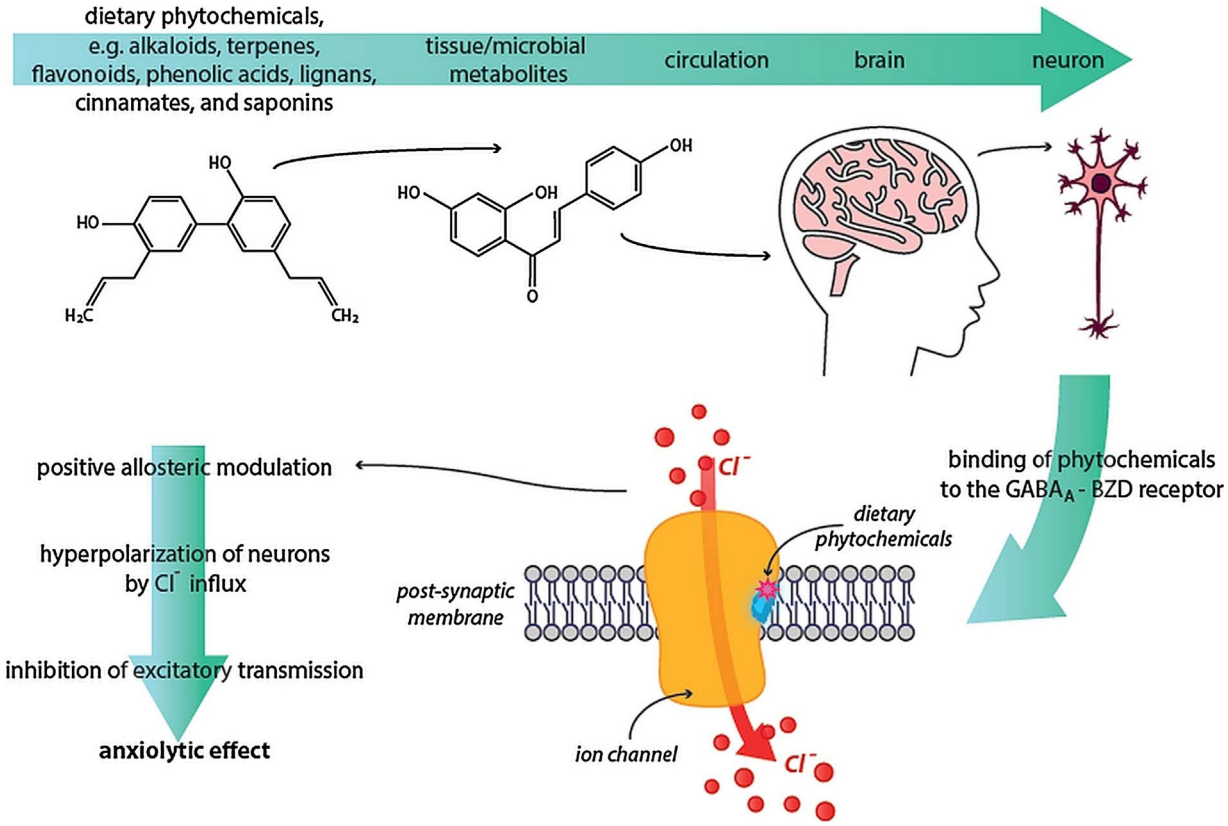

Fig. 3. Phytochemicals as $GABA_A$-BZD receptor ligands with positive allosteric modulations.
Numerous structurally different classes of phytochemicals demonstrate high affinity for the benzodiazepine binding site of the $GABA_A$ receptor complex. Specific plant-derived ligands (such as alkaloids, terpenes, flavonoids, phenolic acids, lignans, cinnamates, or saponins) were described to modulate the $GABA_A$ receptor. These compounds cause membrane hyperpolarization by allowing chloride anion Cl^- influx, which is followed by inhibition of excitatory transmission and reduction of anxiety.
$GABA_A$, gamma-aminobutyric acid type A receptor; BZD, benzodiazepine.

raised the locomotor activity and the exploratory skills in mice [68]. Used compounds demonstrated apparent anxiolytic-like effects, moreover sedative activity and/or compulsive behaviour were not manifested [68]. Using the light/dark box and the open field test in a mouse model, the anxiolytic potential of *Vitis vinifera* L. juice (VVJ) was evaluated. VVJ was administered to mice orally by gavage at a dose of 4 and 8 mL/kg b.w. VVJ, rich in flavonoids and stillbenoids, increased (dose-dependently) the time spent in light cubicle, the transfer latency from the light to dark cubicle, the number of transitions between the two cubicles. Moreover, using open field test, VVJ caused the increase in ambulation and rearing in mice. Authors of this study suggested the anxiolytic-like characteristics of VVJ in animal anxiety model [85]. Li et al. [86] demonstrated that repeated treatment of mice with flavonoid quercitrin (5.0 and 10.0 mg/kg/day, p.o.) for seven days raised the percentage of entries into and also increased the time spent on the open arms of the elevated plus maze in comparison with the control group. In the light/dark box and the marble-burying tests, quercitrin exerted an anxiolytic-like effect using both doses. Moreover, quercitrin did not change the spontaneous locomotor activity. Authors concluded that activities of quercitrin might be mediated through $5\text{-}HT_{1A}$ receptors; however, benzodiazepine site of $GABA_A$ receptor is not included in the signalling [86]. Luteolin (2-(3,4-Dihydroxyphenyl)- 5,7-dihydroxy-4-chromenone), another flavonoid, has been documented as a compound which is probably involved in the modulation of $GABA_A$ receptor signalling, and through this mechanism manifests an antidepressant, ant nociceptive, and anxiolytic-like characteristics. Using the mice model, luteolin inhibited $GABA_A$-mediated currents and with various degrees of potency and efficacy also activated the kinetics of recombinant $\alpha1\beta2$, $\alpha1\beta2\gamma2$, $\alpha5\beta2$, and $\alpha5\beta2\gamma2$ receptors. Authors concluded that luteolin demonstrated negative regulatory effects on both recombinant and endogenous $GABA_A$ receptors and restrained phasic rather than tonic inhibition in the hippocampus [87]. Significant anxiolytic effects of isolated flavonoids including xanthones [88] and spinosin [89] or whole natural substances rich in flavonoids [90–93] were demonstrated in other preclinical studies.

Several observations suggest that phenolic acids exhibit anxiolytic activities. Chlorogenic acid is one of the most abundant polyphenols in fruits. Bouayed et al. demonstrated that chlorogenic acid assigns anxiolytic activity in the model of anxiety in mice using the light/dark test, the elevated plus maze, and the free exploratory test [94]. The anxiolytic-like properties of sinapic acid (phenylpropanoid compound) were examined in the mouse elevated plus-maze and hole-board test. Observed anxiolytic effects were blocked by $GABA_A$ antagonists – flumazenil and bicuculline. In addition, sinapic acid substantially and dose-dependently potentiated GABA current in single cortical neurons. Authors concluded that sinapic acid is a prominent anxiolytic agent [95]. Moreover, cumulative evidence from extensive preclinical research demonstrates that *p*-coumaric acid possess pleiotropic biological effects in organism, including anxiolytic activities [96].

Moreover, lignans, cinnamates, and saponins exhibited apparent anxiolytic effects in preclinical research. The study of Han et al. evaluated the anxiolytic-like effects of 4-O-methylhonokiol, a neolignan compound of *Magnolia officinalis* L., using the mouse model [97]. Authors concluded that 4-O-methylhonokiol showed anxiolytic properties and that this activity may be mediated through $GABA_A$ receptor signalling. Similarly, lignan sesamin suppressed anxiety-like behaviours in the chronic pain mouse model. Investigators noticed that these changes were caused at least partially through the regulation of GABAergic and glutamatergic signalling in the amygdala of animals [98]. Using the mouse model, Korean authors examined effects of 3,4,5-

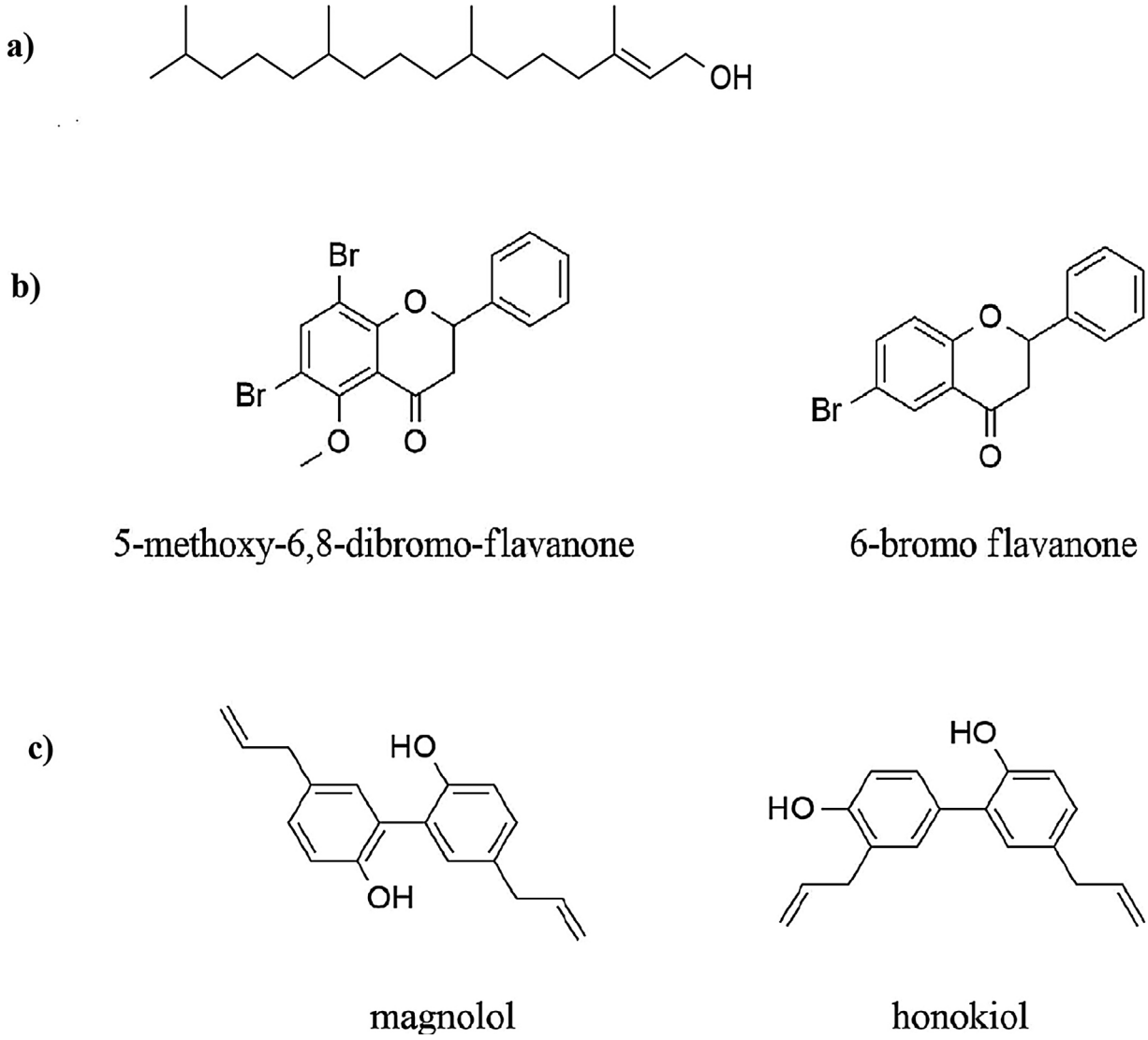

Fig. 4. Chemical structures of different classes of plant natural compounds with anxiolytic effects.
a) diterpene phytol (3,7,11,15-tetrametilhexadec-2-en-1-ol) belong to branched-chain unsaturated alcohols with characteristic structural elements – a single hydroxyl group per molecule and a twenty-one double bond carbon atoms.
b) halogenated flavonoids, 5-methoxy-6, 8-dibromoflavanone and 6-bromoflavanone.
c) biologically active compounds of *Magnolia officinalis* L. with phenol ring, magnolol and honokiol.

trimethoxycinnamic acid on stress-provoked anxiety- and depression-like behaviours in the elevated plus maze and forced swim test. They concluded that the administration of 3,4,5-trimethoxycinnamic acid may provide a potential new strategy for the treatment of anxiety and depression in humans [99]. Similar results of cinnamates on anxiety in rats showed Anderson et al. [100]. Results of Jung et al. demonstrated that anxiolytic-like effects observed in mice after Julibroside C1 (a saponin isolated from *Albizzia julibrissin Durazz* L.) administration may be mediated through the 5-HT1A and $GABA_A$-benzodiazepine receptor systems [101]. In another experiment, polygalasaponin revealed significant anxiolytic and sedative-hypnotic properties with acceptable tolerance on used doses in experimental animals [102].

3. Plant extracts

Except for isolated phytochemicals, there are a plethora of experimental studies testing whole natural substances or extracts as anxiolytics. “Silexan” is a preparation extracted from *Lavandula angustifolia* L. flowers (containing 80 mg lavender essential oil in gelatine capsules), which with clinical efficient in anxiety disorders [103–106]. Using rodent model, Kumar [103] evaluated the anxiolytic effects of intraperitoneally administered “Silexan” at doses of 3, 10, and 30 mg/kg. The effects of “Silexan” were compared with orally administered lorazepam (5 mg/kg) and diazepam (3 mg/kg). All agents were given to animals once daily during 7 consecutive days. After one hour from the last drug or vehicle administration all used dosages of “Silexan” revealed dose-dependent anxiolytic effects in the open-field test, the elevated plus-maze test, the elevated zero-maze test, the social interaction test, and in a novelty-induced suppressed feeding latency test. Observed anxiolytic effects of “Silexan” were similar with the standard anxiolytic drug lorazepam [103]. Moreover, “Silexan” increased pentobarbital-induced sleeping time, but in contrast to diazepam, it did not significantly change the locomotor activity and muscle-grip performance. Kasper et al. reported on the clinical efficacy and tolerability of “Silexan”, with particular attention to subthreshold generalized anxiety disorder (GAD) [104,105]. In this analysis, seven trials (with treatment duration up to 10 weeks) conducting on patients with anxiety or generalized anxiety disorder (GAD) were included. After the 2-week treatment, “Silexan” showed apparent anxiolytic effect in patients. Using the Hamilton Anxiety Scale (HAMA), the score decreased by

10.4 ± 7.1 or 12.0 ± 7.2 points (6th week of treatment) and by 11.8 ± 7.7 or 16.0 ± 8.3 points (10th week of treatment). In addition, the drug demonstrated positive effects on typical co-morbidity signs of anxiety disorders, such as disturbed sleep, somatic complaints, or decreased quality of life. Using daily doses of 80 or 160 mg, "Silexan" was well-tolerated by patients (with exception of mild gastrointestinal symptoms), moreover, it did not cause any drug interactions or withdrawal symptoms [104,106]. Overall, lavender oil showed no sedative effects had no potential for drug abuse; therefore, "Silexan" could be an effective alternative to benzodiazepines.

In another study, mice were treated (p.o.) with the hydroalcoholic extract (0.1–1.1%) of the aerial parts of *Achillea millefoli*um L. which was administered as an acute dose or chronically during 25 days. *Achillea millefolium* L. manifested anxiolytic-like effects without changes in locomotor activity [107]. The doses used (30 and 300 mg/kg) are in the range used in humans (2.43 and 24.3 mg/kg) corresponding to a daily intake of 170 mg or 1.7 g for a person with 70 kg body weight. This dose is close to information provided the National Competent Authorities (2 g dissolved in 250 mL for infusion 1–2 times a day) [108]. Under the same experimental conditions, apigenin alone did not have anxiolytic-like effects, indicating that apigenin was not involved in the anxiolytic-like effects of *Achillea millefolium* L. extract [107]. Overall, the effective doses to induce an anxiolytic-like effect were similar to those used in traditional preparations. Interestingly, the anxiolytic-like effect of *Achillea millefolium* L. occurred after repeated treatment (25 days), suggesting the absence of tolerance to this effect after short-term administration, which is similar to diazepam. Binding data for [3H]-flunitrazepam indicate that GABA/BDZ dependent mechanisms do not mediate these effects. This is an interesting finding since it differentiates *Achillea millefolium* L. from benzodiazepines and other plants extracts with anxiolytic effect in rodents [109–111]. For example, flumazenil, at a dose that does not affect behavioural indices in mice, blocked the anxiolytic-like effect of *Cymbopogon citratus* L. (i.e., increased the time spent in the light compartment in the light/dark test; [112]) and *Passiflora actinina* L. (i.e., increased the percent open arm time and entries in the elevated plus maze; [111]). Methanolic extract of different parts of *Angelica archangelica* L. rendered an anxiolytic-like action in the elevated plus maze, expressed by an increased number of open arm entries and time spent in the elevated plus maze model in a rat model [113]. Also, the behavioural alterations are similar to anxiolytic-like effects, induced by diazepam.

A 70% hydroethanolic extract of leaves of *Cissampelos pareira* L. (*Menispermaceae*) was also successfully used as an anxiolytic. The extract is rich in alkaloids and contains alkaloids, flavanoids, terpenoids and steroids. Anxiolytic-like activity was evaluated by using EPM, light dark model, and forced swim test (FST) models in rats. It was confirmed that the extract of *Cissampelos pareira* L. could potentially be used in the management of anxiety-like behaviour (200 or 400 mg/kg) [114].

Extracts from the bark of *Magnolia officinalis* L. are used as sedatives and anxiolytics in traditional Chinese and Japanese medicine for centuries [115,116]. These extracts have anxiolytic activity in rodents with anxiolytic, sedative, neuroprotective and anti-convulsant actions [115,117]. Two clinical studies found that they reduce temporary anxiety and improve sleep [118,119]. The isomers magnolol (5,5′-diallyl-2,2′-dihydroxybiphenyl) and honokiol (3,5′-diallyl-4,2′-dihydroxybiphenyl) (Fig. 4c) are the active components (1–10% of the dried bark, depending upon species and isolation method) [115,116]. Both magnolol and honokiol bind to and modulate $GABA_A$ receptors [120]. Other studies reported that magnolol and honokiol can modestly inhibit dopamine transporter activity and reduce the binding to dopamine (D_5) and serotonin ($5HT_6$) receptors in vitro [121]. There is also preclinical evidence for their inhibition of glutamate receptors [122,123] and that honokiol derivatives enhances the activity of $GABA_C$ receptors in cultured rat hippocampal neurons [124].

Methanol extract of *Achyranthes aspera* L. (MEAA) (*Amaranthaceae*) has an anxiolytic-like effect in male swiss albino mice [125] in doses of 100, 300 and 600 mg/kg p.o. Hole board (HB), open field (OF), elevated plus maze (EPM) and light/dark exploration (LDE) tests were used for the determination of anxiolytic-like activity. MEAA exhibited anxiolytic-like activity which was attributed to its phyto-constituents, such as alkaloids, steroids and triterpenes. In another study, anti-anxiety effects of methanol extract of *Alternanthera brasiliana* L. (MEAB) Kuntze, was evaluated using BB, OF, EPM and LDE test in mice. Results showed significant anxiolytic activity of MEAB in rodent models. Authors suggested that these effects might be accredited to different phytochemicals like alkaloids, steroids and triterpenes present in MEAB [126]. Also *Drymaria cordata* L. hydroethanolic extract (25, 50 and 100 mg/kg; p.o.) possessed anxiolytic-like activity in HB, OFT, EPM and the LDE in mice [127]. Phytochemicals such as triterpenes, diterpenes, steroids and tannins are suggested to contribute to these anxiolytic-like activity.

In the study with male mice, *Aniliaeea Panax quinquefolium* L. (PQS) rich in saponins, demonstrated anxiolytic-like effects similar to diazepam [128]. In the EPM PQS (50 mg/kg, p.o.) plus diazepam (2.5 mg/kg, p.o.) increased the time and entries in open arms. In the LDE test, PQS (50 and 100 mg/kg, p.o.) and diazepam (2.5 mg/kg, p.o.) prolonged the time spent in light. In the hole-board test, PQS (50 and 100 mg/kg, p.o.) and diazepam increased both head-dip counts and head-dip duration. Both PQS and diazepam decreased fighting time in the isolation-induced aggressive test [128]. Since PQS, in contrast to diazepam, has no effect on locomotion, it could offer less side effects. The findings suggest that PQS is a potential candidate for an anxiolytic drug. The most popular plants with proved anxiolytic-like efficacy in the preclinical studies are summarized in Table 1.

The most recent papers demonstrated anxiolytic effects of *Lippia graveolens* L. [129], *Lavandula officinalis* L. [130], *Trigonella foenum-graecum* L. seeds [131], *Tanacetum parthenium* L. [132], *Elettaria cardamomum* L. [133], *Caesalpinia digyna Rottler* L. roots [134], Xiao Yao San [135] or *Cocos nucifera* L. [136] in preclinical research. There are also several recent clinical evaluations focusing on anxiolytic effects of plant extracts. The aim of the first study was to investigate the effects of *Humulus lupulus* L. plant (hops) dry extract on self-reported depression, anxiety and stress levels in young adults (36 participants) in a randomized, placebo-controlled, double-blind, crossover pilot study. Over a 4-week period of treatment, hops (two 200 mg capsules once daily) significantly decreased anxiety score (9.2 ± 7.3 vs. 5.1 ± 5.9) and moreover, decreases in depression (9.2 ± 7.3 vs. 5.1 ± 5.9) and stress (11.9 ± 7.9 vs. 9.2 ± 7.4) scores were documented with hops [137]. Enrolling 179 participants, Mao et al. evaluated the long-term chamomile (*Matricaria chamomilla* L., 1500 mg daily in three doses) use for the prevention of generalized anxiety disorder symptom relapse in a double-blind randomized controlled trial. Results showed that long-term chamomile administration was safe and significantly reduced moderate-to-severe generalized anxiety disorder symptoms ($P = 0.0032$), but did not significantly reduce rate of relapse (hazard ratio, 0.52; 95% CI, 0.20–1.33; $P = 0.16$) [138]. Mazidi et al. [139] assessed the anti-anxiety and anti-depression effects of saffron extract (*Crocus sativus* L.) using sixty participants in a 12-week double-blind, placebo-controlled trial design. Saffron supplements (50 mg saffron capsule) demonstrated significant effect on the beck anxiety inventory and beck depression inventory questionnaires scores in subjects compared to placebo ($P < 0.001$).

Identification of compounds with anxiolytic effects from plants may provide new treatment options [140]. Moreover, such preparations could be an economical therapeutic alternative.

4. Conclusion

Anxiety remains a major public health problem which is difficult to treat. The traditional treatments have limitations and the number of users with dependance is increasing. This review highlights the search for new medication to treat anxiety in order to improve conventional

Table 1
The most common plants with proved anxiolytic-like efficacy using rodent models.

Medicinal plant	Composition with possible anxiolytic-like action	Experimental tests	References
Achillea millefolium	Not certainly determine	EPM Marble-burying test OFT	Baretta et al., 2012
Achyranthes aspera	alkaloids, steroids, triterpenes	EPM OFT Light/dark test Hole-board test	Barua et al., 2012
Alternanthera brasiliana	alkaloids, steroids, triterpenes	EPM OFT Light/dark test Hole-board test	Barua et al., 2013
Angelica archangelica	furanocoumarins, selimone, archangelin, oxypeucedanin, lycoside, psoralen, bergapten	EPM OFT	Kumar and Bhat, 2011
Cissampelos pareira	alkaloids, flavanoids, terpenoids, steroids	EPM FST Light/dark test	Thakur, Rana, 2013
Drymaria cordata	triterpens, diterpens, steroids	EPM OFT Light/dark test Hole-board test	Barua et al., 2009
Lavandula angustifolia	essential oil	Elevated zero-maze test Social interaction test OFT Suppressed feeding latency test	Kumar, 2013
Magnolia officinalis	magnolol, honokiol	EPM Marble-burying test OFT	Alekssev et al.
Panax quinque	saponins	EPM OFT Light/dark test Hole-board test	Wei et al., 2007

therapies. New plant natural compounds or plant extracts are under investigation in order to find a better and safer alternative. Currently, several classes of phytochemicals may be considered as supplements to conventional anxiolytic therapies in order to improve efficacy and reduce adverse effects. While the results are encouraging in plant-derived natural substances, further research is needed in order to elucidate the structure-activity relationships, metabolism, absorption, and neuro-psycho-pharmacological mechanisms of these phytochemicals. However, as the majority of studies are in animal models, validation of the therapeutic effects of new molecules in anxiety-like disorders in humans warrants clinical evaluation.

Conflict of interest

Authors declare no conflict of interest.

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References

[1] H.U. Wittchen, I. Heinig, K. Beesdo-Baum, Anxiety disorders in DSM-5: an overview on changes in structure and content, Nervenarzt 85 (2014) 548–552.
[2] R.C. Kessler, W.T. Chiu, O. Demler, K.R. Merikangas, E.E. Walters, Prevalence severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication, Arch. Gen. Psychiatry 62 (2005) 617–627.
[3] R.C. Kessler, M. Angermeyer, J.C. Anthony, R. De Graaf, K. Demyttenaere, I. Gasquet, G. De Girolamo, S. Gluzman, O. Gureje, J.M. Haro, N. Kawakami, A. Karam, D. Levinson, M.E. Medina Mora, M.A. Oakley Browne, J. Posada-Villa, D.J. Stein, C.H. Adley Tsang, S. Aguilar-Gaxiola, J. Alonso, S. Lee, S. Heeringa, B.E. Pennell, P. Berglund, M.J. Gruber, M. Petukhova, S. Chatterji, T.B. Ustün, Lifetime prevalence and age of onset distributions of mental disorders in the World Health Organization’s World Mental Health Survey Initiative, World. Psychiatry 6 (2007) 168–176.
[4] E. Martín-Merino, A. Ruigómez, M.A. Wallander, S. Johansson, L.A. García-Rodríguez, Prevalence, incidence, morbidity and treatment patterns in a cohort of patients diagnosed with anxiety in UK primary care, Fam. Pract. 27 (2010) 9–16.
[5] J.M. Somers, E.M. Goldner, P. Waraich, L. Hsu, Prevalence and incidence studies of anxiety disorders: a systematic review of the literature, Can. J. Psychiatry. 51 (2006) 100–113.
[6] B. Bandelow, S. Michaelis, Epidemiology of anxiety disorders in the 21 st century, Dialogues Clin. Neurosci. 17 (2015) 327–335.
[7] D.J. Oathes, B. Patenaude, A.F. Schatzberg, A. Etkin, Neurobiological signatures of anxiety and depression in resting-state functional magnetic resonance imaging, Biol. Psychiatry. 77 (2015) 385–393.
[8] J.E. LeDoux, Feelings what are they & how does the brain make them? Daedalus 144 (2015) 96–111.
[9] M. Bertilsson, J. Löve, G. Ahlborg Jr., G. Hensing, Health care professionals' experience-based understanding of individuals' capacity to work while depressed and anxious, Scand. J. Occup. Ther. 22 (2015) 126–136.
[10] L.C. Hellström, L.F. Eplov, M. Nordentoft, S.D. Østergaard, P. Bech, The Diagnostic Apathia Scale predicts the ability to return to work following depression or anxiety, Acta. Neuropsychiatr. 26 (2014) 364–371.
[11] M.E. Coles, J.R. Schubert, R.G. Heimberg, B.D. Weiss, Disseminating treatment for anxiety disorders: step 1: Recognizing the problem as a precursor to seeking help, J. Anxiety. Disord. 28 (2014) 737–740.
[12] J. Sun, Z. Li, N. Buys, E.A. Storch, Correlates of comorbid depression, anxiety and helplessness with obsessive-compulsive disorder in Chinese adolescents, J. Affect. Disord. 174 (2015) 31–37.
[13] C.D. Sherbourne, G. Sullivan, M.G. Craske, P. Roy-Byrne, D. Golinelli, R.D. Rose, D.A. Chavira, A. Bystritsky, M.B. Stein, Functioning and disability levels in primary care out-patients with one or more anxiety disorders, Psychol. Med. 40 (2010) 2059–2068.
[14] T.W. Strine, A.H. Mokdad, L.S. Balluz, O. Gonzalez, R. Crider, J.T. Berry, K. Kroenke, Depression and anxiety in the United States: findings from the 2006 behavioral risk factor surveillance system, Psychiatr. Serv. 59 (2008) 1383–1390.
[15] A. Schaffer, J. Cairney, A. Cheung, S. Veldhuizen, A. Levitt, Community survey of bipolar disorder in Canada: lifetime prevalence and illness characteristics, Can. J. Psychiatry 51 (2006) 9–16.
[16] R.C. Kessler, P. Berglund, O. Demler, R. Jin, D. Koretz, K.R. Merikangas, A.J. Rush, E.E. Walters, P.S. Wang, National comorbidity survey replication, the epidemiology of major depressive disorder: results from the national comorbidity survey replication (NCS-R), JAMA 289 (2003) 3095–3105.
[17] R.C. Kessler, L. Adler, R. Barkley, J. Biederman, C.K. Conners, O. Demler, S.V. Faraone, L.L. Greenhill, M.J. Howes, K. Secnik, T. Spencer, T.B. Ustun, E.E. Walters, A.M. Zaslavsky, The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication, Am. J. Psychiatry 163 (2006) 716–723.
[18] Canadian Psychiatric Association, Clinical practice guidelines: management of anxiety disorders, Can. J. Psychiatry 51 (2006) (9S-91S.).
[19] S.E. Bruce, J.T. Machan, I. Dyck, M.B. Keller, Infrequency of pure GAD: impact of psychiatric comorbidity on clinical course, Depress. Anxiety 14 (2001) 219–225.
[20] M.K. Hofmeijer-Sevink, N.M. Batelaan, H.J. van Megen, B.W. Penninx, D.C. Cath, M.A. van den Hout, A.J. van Balkom, Clinical relevance of comorbidity in anxiety disorders: a report from the Netherlands Study of Depression and Anxiety (NESDA), J. Affect. Disord. 137 (2012) 106–112.
[21] K.R. Boylan, P.J. Bieling, M. Marriott, H. Begin, L.T. Young, G.M. MacQueen, Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder, J. Clin. Psychiatry 65 (2004) 1106–1113.
[22] S. Shankman, D. Klein, The impact of comorbid anxiety disorders on the course of dysthymic disorder: a 5-year prospective longitudinal study, J. Affect. Disord. 70 (2002) 211–217.
[23] C.S. Mackenzie, K. Reynolds, J. Cairney, D.L. Streiner, J. Sareen, Disorder-specific mental health service use for mood and anxiety disorders: associations with age, sex, and psychiatric comorbidity, Depress. Anxiety 29 (2012) 234–242.
[24] T. McLaughlin, E. Geissler, G. Wan, Comorbidities and associated treatment charges in patients with anxiety disorders, Pharmacotherapy 23 (2003) 1251–1256.
[25] J. Sareen, F. Jacobi, B.J. Cox, S.L. Belik, I. Clara, M.B. Stein, Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions, Arch. Intern. Med. 166 (2006) 2109–2116.
[26] H.U. Wittchen, Generalized anxiety disorder: prevalence, burden, and cost to society, Depress. Anxiety 16 (2002) 162–171.
[27] G. Waghorn, D. Chant, P. White, H. Whiteford, Disability, employment and work performance among people with ICD-10 anxiety disorders, Aust. N. Z. J. Psychiatry 39 (2005) 55–56.
[28] K. Kroenke, R.L. Spitzer, J.B. Williams, P.O. Monahan, B. Löwe, Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection, Ann. Intern. Med. 146 (2007) 317–325.
[29] P. Nuss, Anxiety disorders and GABA neurotransmission: a disturbance of modulation, Neuropsychiatr. Dis. Treat. 11 (2015) 165–175.
[30] A. Locci, G. Pinna, Neurosteroid biosynthesis downregulation and changes in GABAA receptor subunit composition: a biomarker axis in stress-induced cognitive and emotional impairment, Br. J. Pharmacol. (April) (2017), http://dx.doi.org/10.1111/bph.13843 (Epub ahead of print).
[31] R. Pizzo, O.F. O'Leary, J.F. Cryan, Elucidation of the neural circuits activated by a

GABA$_B$ receptor positive modulator: relevance to anxiety, Neuropharmacology S0028–S3908 (17) (2017) 30352, http://dx.doi.org/10.1016/j.neuropharm.2017.07.021 [Epub ahead of print].
[32] H.C. Chua, M. Chebib, GABA$_A$ receptors and the diversity in their structure and pharmacology, Adv. Pharmacol. 79 (2017) 1–34.
[33] N. Wongsamitkul, R. Baur, E. Sigel, Toward understanding functional properties and subunit arrangement of α4β2δ γ-Aminobutyric acid, type a (GABAA) receptors, J. Biol. Chem. 291 (2016) 18474–18483.
[34] K. Löw, F. Crestani, R. Keist, D. Benke, I. Brünig, J.A. Benson, J.M. Fritschy, T. Rülicke, H. Bluethmann, H. Möhler, U. Rudolph, Molecular and neuronal substrate for the selective attenuation of anxiety, Science 290 (2000) 131–134.
[35] G. Perna, A. Alciati, A. Riva, W. Micieli, D. Caldirola, Long-Term pharmacological treatments of anxiety disorders: an updated systematic review, Curr. Psychiatry Rep. 18 (2016) 23.
[36] M.J. Bucx, P. Krijtenburg, M. Kox, Preoperative use of anxiolytic-sedative agents; are we on the right track, J. Clin. Anesth. 33 (2016) 135–140.
[37] C.B. Rosnick, J.L. Wetherell, K.S. White, C. Andreescu, D. Dixon, E.J. Lenze, Cognitive-behavioral therapy augmentation of SSRI reduces cortisol levels in older adults with generalized anxiety disorder: a randomized clinical trial, J. Consult. Clin. Psychol. 84 (2016) 345–352.
[38] K. Mitte, P. Noack, R. Steil, M. Hautzinger, A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder, J. Clin. Psychopharmacol. 25 (2005) 141–150.
[39] C.M. Cunningham, G.E. Hanley, S. Morgan, Patterns in the use of benzodiazepines in British Columbia: examining the impact of increasing research and guideline cautions against long-term use, Health. Policy 97 (2010) 122–129.
[40] B. Dell'osso, M. Lader, Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal, Eur. Psychiatry 28 (2013) 7–20.
[41] H. Nishikawa, T. Inoue, T. Izumi, T. Koyama, Synergistic effects of tandospirone and selective serotonin reuptake inhibitors on the contextual conditioned fear stress response in rats, Eur. Neuropsychopharmacol. 17 (2007) 643–650.
[42] E.M. Tsapakis, Z. Gamie, G.T. Tran, S. Adshead, A. Lampard, A. Mantalaris, E. Tsiridis, The adverse skeletal effects of selective serotonin reuptake inhibitors, Eur. Psychiatry 27 (2012) 156–169.
[43] N.S. Burghardt, E.P. Bauer, Acute and chronic effects of selective serotonin reuptake inhibitor treatment on fear conditioning: implications for underlying fear circuits, Neuroscience 247 (2013) 253–272.
[44] E.M. Haney, S.J. Warden, M.M. Bliziotes, Effects of selective serotonin reuptake inhibitors on bone health in adults: time for recommendations about screening, prevention and management? Bone 46 (2010) 13–17.
[45] J.D. Olivier, T. Blom, T. Arentsen, J.R. Homberg, The age- dependent effects of selective serotonin reuptake inhibitors in humans and rodents: a review, Prog. Neuropsychopharmacol. Biol. Psychiatry 35 (2011) 1400–1408.
[46] P. Longone, F. diMichele, E. D'Agati, E. Romeo, A. Pasini, R. Rupprecht, Neurosteroids as neuromodulators in the treatment of anxiety disorders, Front. Endocrinol. (Lausanne) 19 (2011) 55.
[47] A. Colasanti, E.A. Rabiner, A. Lingford-Hughes, D.J. Nutt, Opioids and anxiety, J. Psychopharmacol. 25 (2011) 1415–1433.
[48] E.J. Lin, Neuropeptides as therapeutic targets in anxiety disorders, Curr. Pharm. 18 (2012) 5709–5727.
[49] J.M. Wierońska, A. Pilc, Glutamate-based anxiolytic ligands in clinical trials, Expert Opin. Investig. Drugs. 22 (2013) 1007–1022.
[50] T. Rubino, M. Sala, D. Viganò, D. Braida, C. Castiglioni, V. Limonta, C. Guidali, N. Realini, D. Parolaro, Cellular mechanisms underlying the anxiolytic effect of low doses of peripheral Delta9-tetrahydrocannabinol in rats, Neuropsychopharmacology 32 (2007) 2036–2045.
[51] F. Berrendero, R. Maldonado, Involvement of the opioid system in the anxiolytic-like effects induced by Delta(9)-tetrahydrocannabinol, Psychopharmacology (Berl) 163 (2002) 111–117.
[52] K.A. Emmitte, Recent advances in the design and development of novel negative allosteric modulators of mGlu5, ACS. Chem. Neurosci. 2 (2011) 411–432.
[53] L.B. Nicolas, Y. Kolb, E.P. Prinssen, A combined marble burying-locomoter activity test in mice: a practical screening test with sensitivity to different classes of anxiolytics and antidepressants, Eur. J. Pharmacol. 547 (2006) 106–115.
[54] C.S. Busse, J. Brodkin, D. Tattersall, J.J. Anderson, N. Warren, L. Tehrani, L.J. Bristow, M.A. Varney, N.D. Cosford, The behavioral profile of the potent and selective mGlu5 receptor antagonist 3-(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) in rodent models of anxiety, Neuropsychopharmacology 29 (2004) 1971–1979.
[55] M. Pietraszek, I. Sukhanov, P. Maciejak, J. Szyndler, A. Gravius, A. Wisłowska, A. Płaźnik, A.Y. Bespalov, W. Danysz, Anxiolytic-like effects of mGlu1 and mGlu5 receptor antagonists in rats, Eur. J. Pharmacol. 514 (2005) 25–34.
[56] A. Baron, E. Lingueglia, Pharmacology of acid-sensing ion channels – Physiological and therapeutical perspectives, Neuropharmacology 94 (2015) 19–35.
[57] G.M. Gomes, C.F. Mello, M.M. da Rosa, G.V. Bochi, J. Ferreira, S. Barron, M.A. Rubin, Polyaminergic agents modulate contextual fear extinction in rats, Neurobiol. Learn. Mem. 93 (2010) 589–595.
[58] K. Lewellyn, D. Bialonska, M.J. Loria, S.W. White, K.J. Sufka, J.K. Zjawiony, In vitro structure-activity relationships of aplysinopsin analogs and their in vivo evaluation in the chick anxiety-depression model, Bioorg. Med. Chem. 21 (2013) 7083–7090.
[59] A.C. Campos, M.V. Fogaça, D.C. Aguiar, F.S. Guimarães, Animal models of anxiety disorders and stress, Rev. Bras. Psiquiatr. 35 (2013) S101–111.
[60] M. Bourin, Animal models for screening anxiolytic-like drugs: a perspective, Dialogues Clin. Neurosci. 17 (2015) 295–303.
[61] M. Komada, K. Takao, T. Miyakawa, Elevated plus maze for mice, J. Vis. Exp. 22 (2008) 1088.
[62] M. Bourin, M. Hascoët, The mouse light/dark box test, Eur. J. Pharmacol. 463 (2003) 55–65.
[63] L. Prut, C. Belzung, The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review, Eur. J. Pharmacol. 463 (2003) 3–33.
[64] A. Can, D.T. Dao, M. Arad, Ch.E. Terrillion, S.C. Piantadosi, T.D. Gould, The mouse forced swim test, J. Vis. Exp. 59 (2012) 3638.
[65] M.J. Millan, M. Brocco, The Vogel conflict test: procedural aspects, gamma-aminobutyric acid, glutamate and monoamines, Eur. J. Pharmacol. 463 (2003) 67–96.
[66] P.M. Barnes, B. Bloom, R. Nahin, Complementary and alternative medicine use among adults and children: united States, 2007 CDC National Health Statistics Report 12 (2008) 1–4.
[67] S.E. Lakhan, K.F. Vieira, Nutritional and herbal supplements for anxiety and anxiety-related disorders: systematic review, Nutr. J. 9 (2010) 42.
[68] E. Ognibene, P. Bovicelli, W. Adriani, L. Saso, G. Laviola, Behavioral effects of 6-bromoflavanone and 5-methoxy-6,8-dibromoflavanone as anxiolytic compounds, Prog. Neuropsychopharmacol. Biol. Psychiatry. 32 (2008) 128–134.
[69] Z.J. Zhang, Therapeutic effects of herbal extracts and constituents in animal models of psychiatric disorders, Life. Sci. 75 (2004) 1659–1699.
[70] A.F. de Brito, J.L. Martins, J.O. Fajemiroye, P.M. Galdino, T.C. De Lima, R. Menegatti, E.A. Costa, Central pharmacological activity of a new piperazine derivative: 4-(1-Phenyl-1h-pyrazol-4- ylmethyl)-piperazine-1-carboxylic acid ethyl ester, Life. Sci. 90 (2012) 910–916.
[71] I.A. Oyemitan, C.A. Elusiyan, M.A. Akanmu, T.A. Olugbade, Hypnotic, anticonvulsant and anxiolytic effects of 1-nitro-2-phenylethane isolated from the essential oil of Dennettia tripetala in mice, Phytomedicine 20 (2013) 1315–1322.
[72] Y.V. Nesterova, T.N. Povet'eva, N.I. Suslov, E.E. Shults, G.N. Ziuz'kov, S.G. Aksinenko, O.G. Afanas'eva, A.V. Krapivin, T.G. Kharina, Anxiolytic activity of diterpene alkaloid songorine, Bull. Exp. Biol. Med. 159 (2015) 620–622.
[73] A.I. Arcos-Martínez, O.D. Muñoz-Muñiz, M.Á. Domínguez-Ortiz, M.V. Saavedra-Vélez, M. Vázquez-Hernández, M.G. Alcántara-López, Anxiolytic-like effect of ethanolic extract of Argemone mexicana and its alkaloids in Wistar rats, Avicenna. J. Phytomed. 6 (2016) 476–488.
[74] A.S. Melo, M.C. Monteiro, J.B. da Silva, F.R. de Oliveira, J.L. Vieira, M.A. de Andrade, A.C. Baetas, J.T. Sakai, F.A. Ferreira, P.J. Cunha Sousa, S. Maia Cdo, Antinociceptive, neurobehavioral and antioxidant effects of Eupatorium triplinerve Vahlonrats, J. Ethnopharmacol. 147 (2013) 293–301.
[75] R. Russo, A. Ciociaro, L. Berliocchi, M.G. Cassiano, L. Rombolà, S. Ragusa, G. Bagetta, F. Blandini, M.T. Corasaniti, Implication of limonene and linalyl acetate in cytotoxicity induced by bergamot essential oil in human neuroblastoma cells, Fitoterapia 89 (2013) 48–57.
[76] A.G. Guimarães, G.F. Oliveira, M.S. Melo, S.C. Cavalcanti, A.R. Antoniolli, L.R. Bonjardim, F.A. Silva, J.P. Santos, R.F. Rocha, J.C. Moreira, A.A. Araújo, D.P. Gelain, L.J. Quintans-Júnior, Bioassay-guided evaluation of antioxidant and antinociceptive activities of carvacrol, Basic. Clin. Pharmacol. Toxicol. 107 (2010) 949–957.
[77] D.G. Machado, M.P. Cunha, V.B. Neis, G.O. Balen, A. Colla, L.E. Bettio, A. Oliveira, F.L. Pazini, J.B. Dalmarco, E.L. Simionatto, M.G. Pizzolatti, A.L. Rodrigues, Antidepressant-like effects of fractions essential oil, carnosol and betulinic acid isolated from Rosmarinus officinalis L, Food. Chem. 136 (2013) 999–1005.
[78] J.P. Costa, G.A. de Oliveira, A.A. de Almeida, M.T. Islam, D.P. de Sousa, R.M. de Freitas, Anxiolytic-like effects of phytol: possible involvement of GABAergic transmission, Brain. Res. 2014 (1547) 34–42.
[79] M.R. Moreira, M.G. Salvadori, A.A. de Almeida, D.P. de Sousa, J. Jordán, P. Satyal, R.M. de Freitas, R.N. de Almeida, Anxiolytic-like effects and mechanism of (−)-myrtenol: a monoterpene alcohol, Neurosci. Lett. 579 (2014) 119–124.
[80] M.M. Bergamaschi, R.H. Queiroz, M.H. Chagas, D.C. de Oliveira, B.S. De Martinis, F. Kapczinski, J. Quevedo, R. Roesler, N. Schröder, A.E. Nardi, R. Martín-Santos, J.E. Hallak, A.W. Zuardi, J.A. Crippa, Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naöve social phobia patients, Neuropsychopharmacology 36 (2011) 1219–1226.
[81] A.P. Schiavon, J.M. Bonato, H. Milani, F.S. Guimarães, R.M. Weffort de Oliveira, Influence of single and repeated cannabidiol administration on emotional behavior and markers of cell proliferation and neurogenesis in non-stressed mice, Prog. Neuropsychopharmacol. Biol. Psychiatry 64 (2016) 27–34.
[82] T.E. Ceremuga, D. Valdivieso, C. Kenner, A. Lucia, K. Lathrop, O. Stailey, H. Bailey, J. Criss, J. Linton, J. Fried, A. Taylor, G. Padron, A.D. Johnson, Evaluation of the anxiolytic and antidepressant effects of asiatic acid a compound from Gotu kola or Centella asiatica, in the male Sprague Dawley rat, AANA. J. 83 (2015) 91–98.
[83] A.R. Colla, J.M. Rosa, M.P. Cunha, A.L. Rodrigues, Anxiolytic-like effects of ursolic acid in mice, Eur. J. Pharmacol. 758 (2015) 171–176.
[84] F.H. Melo, E.T. Venâncio, D.P. de Sousa, M.M. de França Fonteles, S.M. de Vasconcelos, G.S. Viana, F.C. de Sousa, Anxiolytic-like effect of Carvacrol (5-isopropyl-2-methylphenol) in mice: involvement with GABAergic transmission, Fundam. Clin. Pharmacol. 24 (2010) 437–443.
[85] M. Aslam, N. Sultana, Evaluation of anxiolytic-like activity of Vitis vinifera juice in mice, Avicenna. J. Phytomed. 6 (2016) 344–350.
[86] J. Li, Q.T. Liu, Y. Chen, J. Liu, J.L. Shi, Y. Liu, J.Y. Guo, Involvement of 5-HT1A receptors in the anxiolytic-like effects of quercitrin and evidence of the involvement of the monoaminergic system, Evid. Based. Complement. Alternat. Med. 2016 (2016) 6530364.
[87] M.L. Shen, C.H. Wang, R.Y. Chen, N. Zhou, S.T. Kao, D.C. Wu, Luteolin inhibits GABAA receptors in HEK cells and brain slices, Sci. Rep. 6 (2016) 27695.
[88] K. Pytka, E. Żmudzka, K. Lustyk, A. Rapacz, A. Olczyk, A. Gałuszka, A. Waszkielewicz, H. Marona, J. Sapa, F. Barbara, The antidepressant- and anxiolytic-like activities of new xanthone derivative with piperazine moiety in behavioral tests in mice, Indian. J. Pharmacol. 48 (2016) 286–291.
[89] J. Liu, W.M. Zhai, Y.X. Yang, J.L. Shi, Q.T. Liu, G.L. Liu, N. Fang, J. Li, J.Y. Guo, GABA and 5-HT systems are implicated in the anxiolytic-like effect of spinosin in mice, Pharmacol. Biochem. Behav. 128 (2015) 41–49.
[90] S.S. Twinomujuni, J. Oloro, P.E. Alele, Anticonvulsant and anxiolytic activity of the leaf aqueous and ethanolic extracts of Melanthera scandens in a rat model, Afr. J. Pharm. Pharmacol. 10 (2016) 216–222.

[91] M. Noori Ahmad Abadi, M. Mortazavi, N. Kalani, H.Z. Marzouni, W. Kooti, S. Ali-Akbari, Effect of hydroalcoholic extract of Rosmarinus officinalis L. leaf on anxiety in mice, J. Evid. Based. Complementary. Altern. Med. 21 (2016) 85–90.
[92] A. Otify, C. George, A. Elsayed, M.A. Farag, Mechanistic evidence of Passiflora edulis (Passifloraceae) anxiolytic activity in relation to its metabolite fingerprint as revealed via LC-MS and chemometrics, Food. Funct. 6 (2015) 3807–3817.
[93] M.C. Noguerón-Merino, E. Jiménez-Ferrer, R. Román-Ramos, A. Zamilpa, J. Tortoriello, M. Herrera-Ruiz, Interactions of a standardized flavonoid fraction from Tilia americana with Serotoninergic drugs in elevated plus maze, J.Ethnopharmacol 164 (2015) 319–327.
[94] J. Bouayed, H. Rammal, A. Dicko, C. Younos, R. Soulimani, Chlorogenic acid a polyphenol from Prunus domestica (Mirabelle), with coupled anxiolytic and antioxidant effects, J. Neurol. Sci. 262 (2007) 77–84.
[95] B.H. Yoon, J.W. Jung, J.J. Lee, Y.W. Cho, C.G. Jang, C. Jin, T.H. Oh, J.H. Ryu, Anxiolytic-like effects of sinapic acid in mice, Life. Sci. 81 (2007) 234–240.
[96] K. Pei, J. Ou, J. Huang, S. Ou, p-Coumaric acid and its conjugates: dietary sources, pharmacokinetic properties and biological activities, J. Sci. Food. Agric. 96 (2016) 2952–2962.
[97] H. Han, J.K. Jung, S.B. Han, S.Y. Nam, K.W. Oh, J.T. Hong, Anxiolytic-like effects of 4-O-methylhonokiol isolated from Magnolia officinalis through enhancement of GABAergic transmission and chloride influx, J. Med. Food. 14 (2011) 724–731.
[98] H.L. Guo, Y. Xiao, Z. Tian, X.B. Li, D.S. Wang, X.S. Wang, Z.W. Zhang, M.G. Zhao, S.B. Liu, Anxiolytic effects of sesamin in mice with chronic inflammatory pain, Nutr. Neurosci. 19 (2016) 231–236.
[99] Y.H. Leem, S. Oh, 3,4,5-Trimethoxycinnamin acid ameliorates restraint stress-induced anxiety and depression, Neurosci. Lett. 585 (2015) 54–59.
[100] R.A. Anderson, B. Qin, F. Canini, L. Poulet, A. Roussel, Cinnamon counteracts the negative effects of a high fat/high fructose diet on behavior, brain insulin signaling and Alzheimer-associated changes, PLoS One 8 (2013) e83243.
[101] Y.H. Jung, R.R. Ha, S.H. Kwon, S.I. Hong, K.H. Lee, S.Y. Kim, S.Y. Lee, C.G. Jang, Anxiolytic effects of Julibroside C1 isolated from Albizzia julibrissin in mice, Prog. Neuropsychopharmacol. Biol. Psychiatry 44 (2013) 184–192.
[102] Y. Yao, M. Jia, J.G. Wu, H. Zhang, L.N. Sun, W.S. Chen, K. Rahman, Anxiolytic and sedative-hypnotic activities of polygalasaponins from Polygala tenuifolia in mice, Pharm. Biol. 48 (2010) 801–807.
[103] V. Kumar, Characterization of anxiolytic and neuropharmacological activities of Silexan, Wien. Med. Wochenschr. 163 (2013) 89–94.
[104] S. Kasper, An orally administered lavandula oil preparation (Silexan) for anxiety disorder and related conditions: an evidence based review, Int. J. Psychiatry. Clin. Pract. 17 (Suppl 1) (2013) 15–22.
[105] S. Kasper, M. Gastpar, W.E. Müller, H.P. Volz, H.J. Möller, A. Dienel, S. Schläfke, Efficacy and safety of silexan a new, orally administered lavender oil preparation, in subthreshold anxiety disorder − evidence from clinical trials, Wien. Med. Wochenschr. 160 (2010) 547–556.
[106] H. Woelk, S. Schläfke, A multi-center double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder, Phytomedicine 17 (2010) 94–99.
[107] I.P. Baretta, R.A. Felizardo, V.F. Bimbato, M.G. dos Santos, C.A. Kassuya, A. Gasparotto Junior, C.R. da Silva, S.M. de Oliveira, J. Ferreira, R. Andreatini, Anxiolytic-like effects of acute and chronic treatment with Achillea millefolium L. extract, J. Ethnopharmacol. 140 (2012) 46–54.
[108] European Medicines Agency, Assessment Report on *Achillea Millefolium* L., EMA/HMPC/149343/2010, (2011) (Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2011/09/WC500115467.pdf .).
[109] D. Benke, A. Barberis, S. Kopp, K.H. Altmann, M. Schubiger, K.E. Vogt, U. Rudolph, H. Möhler, GABA-A receptors as in vivo substrate for the anxiolytic action of valerenic acid, a major constituent of valerian root extracts, Neuropharmacology 56 (2009) 174–181.
[110] F.S. Duarte, M. Marder, A.A. Hoeller, M. Duzzioni, B.G. Mendes, M.G. Pizzolatti, T.C. De Lima, Anticonvulsant and anxiolytic-like effects of compounds isolated from Polygala sabulosa (Polygalaceae) in rodents: in vitro and in vivo interactions with benzodiazepine binding sites, Psychopharmacology (Berl) 197 (2008) 351–360.
[111] L.F. Lolli, C.M. Sato, C.V. Romanini, B. Villas-Boas Lde, C.A. Santos, R.M. de Oliveira, Possible involvement of GABA A-benzodiazepine receptor in the anxiolytic-like effect induced by Passiflora actinia extracts in mice, J. Ethnopharmacol. 111 (2007) 308–314.
[112] C.A. Costa, D.O. Kohn, V.M. de Lima, A.C. Gargano, J.C. Flório, M. Costa, The GABAergic system contributes to the anxiolytic-like effect of essential oil from Cymbopogon citratus (lemongrass), J. Ethnopharmacol. 137 (2011) 828–836.
[113] D. Kumar, Z.A. Bhat, Anti-anxiety Activity of methanolic extracts of different parts of Angelica archangelica Linn, J. Trad. Complement. Med. 3 (2011) 235–241.
[114] P. Thakur, A.C. Rana, Effect of Cissampelos pareira leaves on anxiety-like behavior in experimental animals, J. Trad. Complement. Med. 3 (2013) 188–193.
[115] Y.J. Lee, Y.M. Lee, C.K. Lee, J.K. Jung, S.B. Han, J.T. Hong, Therapeutic applications of compounds in the Magnolia family, Pharmacol. Ther. 130 (2011) 157–176.
[116] J. Patočka, J. Jakl, A. Strunecká, Expectations of biologically active compounds of the genus Magnolia in biomedicine, J. Appl. Biomed. 4 (2006) 171–178.
[117] C.R. Chen, R. Tan, W.M. Qu, Z. Wu, Y. Wang, Y. Urade, Z.L. Huang, Magnolol, a major bioactive constituent of the bark of Magnolia officinalis, exerts antiepileptic effects via the GABA/benzodiazepine receptor complex in mice, Br. J. Pharmacol. 164 (2011) 1534–1546.
[118] D.S. Kalman, S. Feldman, R. Feldman, H.I. Schwartz, D.R. Krieger, R. Garrison, Effect of a proprietary Magnolia and Phellodendron extract on stress levels in healthy women: a pilot, double-blind, placebo-controlled clinical trial, Nutr. J. 7 (2008) 11.
[119] M. Mucci, C. Carraro, P. Mancino, M. Monti, L.S. Papadia, G. Volpini, C. Benvenuti, Soy isoflavones, lactobacilli Magnolia bark extract, vitamin D3 and calcium. Controlled clinical study in menopause, Minerva. Ginecol. 58 (2006) 323–334.
[120] B. Taferner, W. Schuehly, A. Huefner, I. Baburin, K. Wiesner, G.F. Ecker, S. Hering, Modulation of GABAA-receptors by honokiol and derivative: subtype selectivity and structure-activity relationship, J. Med. Chem. 54 (2011) 5349–5361.
[121] U. Koetter, M. Barrett, S. Lacher, A. Abdelrahman, D. Dolnick, Interactions of Magnolia and Ziziphus extracts with selected central nervous system receptors, J. Ethnopharmacol. 124 (2009) 421–425.
[122] Y.R. Lin, H.H. Chen, C.H. Ko, M.H. Chan, Differential inhibitory effects of honokiol and magnolol on excitatory amino acid-evoked cation signals and NMDA-induced seizures, Neuropharmacology 49 (2005) 542–550.
[123] Y.R. Lin, H.H. Chen, Y.C. Lin, C.H. Ko, M.H. Chan, Antinociceptive actions of honokiol and magnolol on glutamatergic and inflammatory pain, J. Biomed. Sci. 16 (2009) 94.
[124] B. Liu, N. Hattori, N.Y. Zhang, B. Wu, L. Yang, K. Kitagawa, Z.M. Xiong, T. Irie, C. Inagaki, Anxiolytic agent, dihydrohonokiol-B, recovers amyloid β protein-induced neurotoxicity in cultured rat hippocampal neurons, Neurosci. Lett. 384 (2005) 44–47.
[125] C.C. Barua, A. Talukdar, S.A. Begum, P. Borah, M. Lahkar, Anxiolytic activity of methanol leaf extract of Achyranthesaspera Linn in mice using experimental models of anxiety, Indian. J. Pharmacol. 44 (2012) 63–67.
[126] C.C. Barua, S.A. Begum, A.G. Barua, R.S. Borah, M. Lahkar, Anxiolytic and anticonvulsant activity of methanol extract of leaves of Alternanthera brasiliana (L.) Kuntze (Amaranthaceae) in laboratory animals, Indian. J. Exp. Biol. 51 (2013) 450–457.
[127] C.C. Barua, J.D. Roy, B. Buragohain, A.G. Barua, P. Borah, M. Lahkar, Anxiolytic effect of hydroethanolic extract of Drymariacordata L Willd, Indian. J. Exp. Biol. 47 (2009) 969–973.
[128] X.Y. Wei, J.Y. Yang, J.H. Wang, C.F. Wu, Anxiolytic effect of saponins from Panax quinquefolium in mice, J. Ethnopharmacol. 111 (2007) 613–618.
[129] M.E. González-Trujano, L.Y. Hernández-Sánchez, V. Muñoz Ocotero, A. Dorazco-González, P. Guevara Fefer, E. Aguirre-Hernández, Pharmacological evaluation of the anxiolytic-like effects of Lippia graveolens and bioactive compounds, Pharm. Biol. 55 (2017) 1569–1576.
[130] B. Rahmati, Z. Kiasalari, M. Roghani, M. Khalili, F. Ansari, Antidepressant and anxiolytic activity of Lavandula officinalis aerial parts hydroalcoholic extract in scopolamine-treated rats, Pharm. Biol. 55 (2017) 958–965.
[131] T. Assad, R.A. Khan, Effect of methanol extract of Trigonella foenum-graecum L. seeds on anxiety, sedation and motor coordination, Metab. Brain Dis. 32 (2017) 343–349.
[132] J. Cárdenas, V. Reyes-Pérez, M.D. Hernández-Navarro, A.M. Dorantes-Barrón, S. Almazán, R. Estrada-Reyes, Anxiolytic- and antidepressant-like effects of an aqueous extract of Tanacetum parthenium L. Schultz-Bip (Asteraceae) in mice, J. Ethnopharmacol. 22 (2017) 22–30.
[133] Y. Masoumi-Ardakani, H. Mahmoudvand, A. Mirzaei, K. Esmaeilpour, H. Ghazvini, S. Khalifeh, G. Sepehri, The effect of Elettaria cardamomum extract on anxiety-like behavior in a rat model of post-traumatic stress disorder, Biomed. Pharmacother. 87 (2017) 489–495.
[134] J. Singh, A. Kumar, A. Sharma, Antianxiety activity guided isolation and characterization of bergenin from Caesalpinia digyna Rottler roots, J. Ethnopharmacol. 195 (2017) 182–187.
[135] H.B. Zhao, Y.M. Jiang, X.J. Li, Y.Y. Liu, X.H. Bai, N. Li, J.X. Chen, Q. Liu, Z.Y. Yan, F.Z. Zhao, Xiao yao san improves the anxiety-Like behaviors of rats induced by chronic immobilization stress: the involvement of the JNK signaling pathway in the hippocampus, Biol. Pharm. Bull. 40 (2017) 187–194.
[136] E.B. Lima, C.N. de Sousa, L.N. Meneses, Y.F.E. Silva Pereira, N.C. Matos, R.B. de Freitas, N.B. Lima, M.C. Patrocínio, L.K. Leal, G.S. Viana, S.M. Vasconcelos, Involvement of monoaminergic systems in anxiolytic and antidepressive activities of the standardized extract of Cocos nucifera L, J. Nat. Med. 71 (2017) 227–237.
[137] I. Kyrou, A. Christou, D. Panagiotakos, C. Stefanaki, K. Skenderi, K. Katsana, C. Tsigos, Effects of a hops (Humulus lupulus L.) dry extract supplement on self-reported depression, anxiety and stress levels in apparently healthy young adults: a randomized placebo-controlled, double-blind, crossover pilot study, Hormones (Athens).7 16 (2017) 171–180.
[138] J.J. Mao, S.X. Xie, J.R. Keefe, I. Soeller, Q.S. Li, J.D. Amsterdam, Long-term chamomile (Matricaria chamomilla L.) treatment for generalized anxiety disorder: a randomized clinical trial, Phytomedicine 23 (2016) 1735–1742.
[139] M. Mazidi, M. Shemshian, S.H. Mousavi, A. Norouzy, T. Kermani, T. Moghiman, A. Sadeghi, N. Mokhber, M. Ghayour-Mobarhan, G.A. Ferns, A double-blind, randomized and placebo-controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression, J. Complement Integr. Med. 13 (2016) 195–199.
[140] M.H. Farzaei, R. Bahramsoltani, R. Rahimi, F. Abbasabadi, M. Abdollahi, A systematic review of plant-derived natural compounds for anxiety disorders, Curr. Top. Med. Chem. 16 (2016) 1924–1942.