Original Article

An updated review on Phytoconstituents of Anxiolytic Activity: Clinical Significance and Therapeutic Efficacy

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Abstract

This review article focused on anxiety therapy, and its primary objective was to shed light on the possible therapeutic efficacy of the active components investigated in the initial preclinical study. It also encourages the discovery of new antianxiety medications derived from plants. Potential screening of the preclinical research on phytoconstituents' antianxiety effects are also highlighted (in-vitro, in-vivo). PubMed, Clinicaltrials.gov, The Plant List (TPL, www.plantlist.org), and Science Direct were used to learn about the pharmacology of phytoconstituents, the historical applications of medicinal plants for anxiety, and the status of phytoconstituents in clinical inquiry. Search results were supplied that used a specific syntax and were restricted to articles that fulfilled particular parameters. Traditional uses of this medicinal plant include relief from anxiety, which makes sense given that seventy percent or more of the phytoconstituents investigated here functioned predominantly on the GABAergic system. Linalool and hypericin are the two phytoconstituents studied for potential clinical benefit in anxiety. Support for the discovery and development of novel antianxiety drugs derived from medicinal plants comes from both preclinical and clinical research on the phytoconstituents used to treat anxiety and its associated comorbidities. A deeper understanding of the pharmacodynamic and pharmacokinetic picture of phytoconstituents is required to assess their efficacy and safety; additional randomized and controlled clinical trials are required. There should be an assessment of botanical assets as well.

Keywords: Anxiety, Phytoconstituents, Medicinal plants, traditional uses, Pharmacological activity

1. Introduction

Anxiety is worrying about things that might go wrong in the future, but fear is the emotional response to anything that could go wrong right now (1). Distressing both the mind and body, anxiety is characterized by worries and worries (2-4). Figure 1 shows cases of anxiety disorder. Anxiety disorders have become the most common mental health issue in the modern era.

More people suffer from anxiety than diabetes, chronic obstructive pulmonary disease, or arthritis combined. (5, 6). A considerable decrease in quality of life relates to the untreated 20 percent lifetime prevalence of anxiety disorders (7). The amygdala, insula, and dorsomedial prefrontal cortex are all involved in the hyperactive fear circuit seen in people with anxiety disorders. Various empirical investigations have demonstrated that (8).

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Selective serotonin reuptake inhibitors, a class of medicines commonly used to treat anxiety, work by blocking the activity of these circuits in response to threatening stimuli. Benzodiazepines, azapirones, and selective serotonin and norepinephrine reuptake inhibitors can be added to this list (9). Nevertheless, benzodiazepines are suggested for up to 94% of those suffering from anxiety disorders (10).

These drugs improve gamma-aminobutyric acid(GABA)inhibition of neuronal activity. This points to the involvement of GABA (A) ionotropic receptors in the central nervous system (CNS) in the medicines' actions. The primary therapeutic benefits of this drug are sedation, hypnosis, anterograde amnesia, reduced anxiety, anticonvulsant action, and centrally mediated muscular relaxation (11). Benzodiazepines can help reduce the symptoms of anxiety disorders, but they also come with a host of unwanted side effects and can even become habit-forming. This has led to the bulk of their indications being reserved for "last resort" medications. Therefore, scientists have been hunting for a natural supplement that can change neurotransmitters while reducing the risk of adverse effects in individuals with anxiety. Anxiety disorders can be helped by using alternative treatments, provided they are both safe and supported by scientific evidence. Over the past two decades, there has been a dramatic increase in the worldwide use of herbal medicines.

According to the WHO, eighty percent of the world's population relies on herbal medicines as their first line of treatment (12). Because of their lower side-effect risks, increased safety, and simplified administration, herbal formulations are chosen over raw plant components and extracts. Since these formulations effectively improve patients' health, they are routinely prescribed for various diseases and disorders that diminish individuals' standard of living. Recent research has shown that herbal medications may effectively treat anxiety disorders with fewer side effects than conventional treatments. This paper provides an up-to-date look at the preclinical research on the potential of various phytoconstituents to reduce anxiety via various signaling pathways. It also provides context for the various anxiolytic phytoconstituents by discussing the historical application of medicinal plants to treat anxiety. Phytoconstituents' status in human medicinal studies is discussed in further detail. This piece aims to justify using phytoconstituents as a therapeutic alternative by reviewing their pharmacology and antianxiety potential.

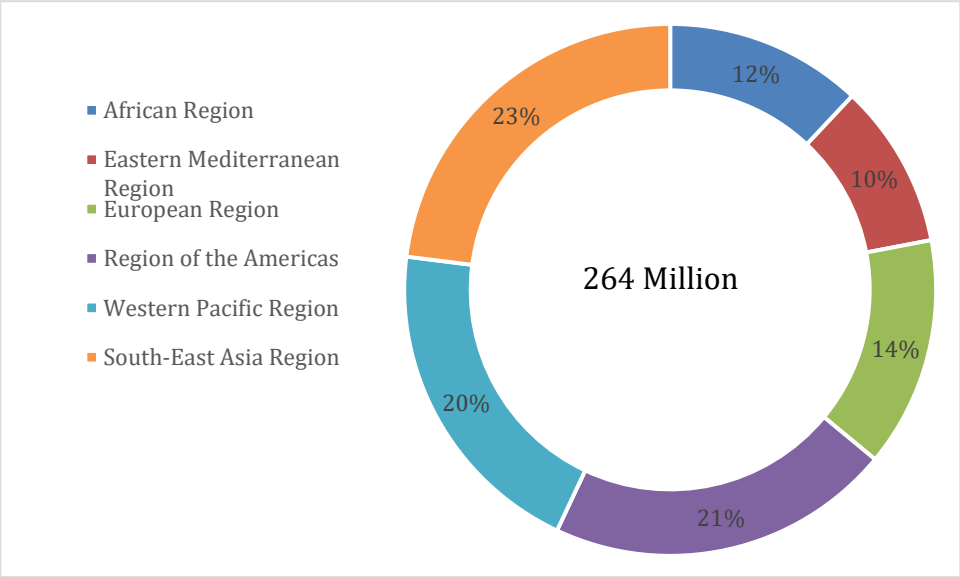


Figure 1 Cases of an anxiety disorder (millions)

1.1 Pathophysiology of anxiety

Anxiety and the potential health problems it can bring on are theorized to have their origins in central nervous system modulation issues. Anxiety disorders have been linked to the chronic dysregulation of brain networks, including cortical and subcortical areas, and this has been observed in animals and humans (amygdala, hippocampus, thalamus, prefrontal, and cingulate cortex). Weaker inhibitory GABAergic transmission in the brain has been linked to anxiety. Ligands regulate chloride selectivity at the GABAA receptor. The protein consists of five different subunits that form a hetero-oligomer and can traverse the neuronal membrane. Most GABAA receptors have a trimeric structure with two identical subunits and a single, non-identical subunit. The subunit increases the likelihood of channel opening in response to GABA by interacting inside the interface between the subunits, whereas the subunit allows GABA binding and confers sensitivity to benzo[a]pyrene (BZD). At least two GABA molecules are required to activate this chloride/bicarbonate-permeable channel, inducing an inflow of negatively charged chloride ions and temporarily reducing the neuron's ability to generate action potentials, resulting in phasic inhibition. Drugs that bind to the GABAA receptor have an anxiolytic effect via enhancing GABA's neuronal inhibitory effects by facilitating chloride channel opening

(13, 14).

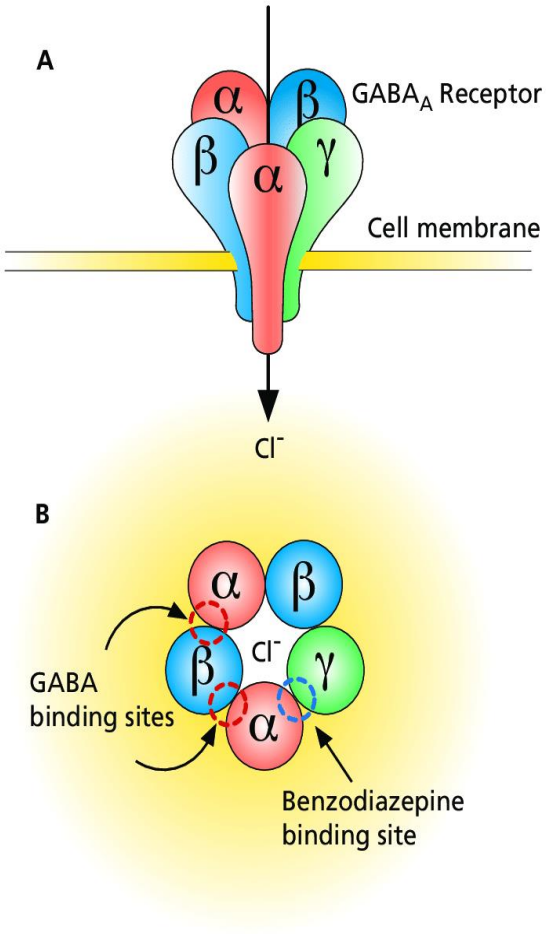


Figure 1 Role of GABA receptor in the pathophysiology of anxiety

1.2 Anxiolytics drugs and mechanism of action

Anxiolytics, the class of drugs used to treat anxiety, used to be called minor tranquilizers. Pharmaceuticals are prescribed to people with neuroses and mild depression to alleviate symptoms such as anxiety, sleeplessness, and difficulty concentrating. Because of their potential for habituation and addiction, these medicines are reserved for usage in exceptional circumstances. Many neurotransmitters, including serotonin, GABA, and nor-epinephrine, contribute to the regulation of anxiety. When serotonin is secreted from nerve terminals, it attaches to a certain receptor, which then controls certain brain functions. Anxiety is brought on by a lack of serotonin. Autonomic arousal processes of anxiety disorders, in particular panic attacks, are modulated by decreased levels of nor-epinephrine in the brain. The selective method for treating anxiety disorders involves the use of drugs like selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors.

Benzodiazepines, barbiturates, benzodiazepine antagonists, and other hypnotic agents are some of the many antianxiety medications available. Anxiety medications work by activating the GABA receptor, which opens the chloride channel and increases the penetration of chloride ions through it. However, the negative charge generated by the chloride channels is neutralized by the presence of potassium ions, which maintains the body's typical physiology. However, when an antianxiety drug opens GABA channels, chloride channels penetrate deeper inside the cell, resulting in a greater negative charge and a correspondingly greater polarization; since this polarization is significantly longer than usual, it is also known as hyperpolarization [Figure 1]. The postsynaptic potential is shifted away from the action threshold, and action potential is suppressed when hyperpolarization delays the depolarization stage. These additional effects of benzodiazepine medications are evaluated together with their antianxiety effects.

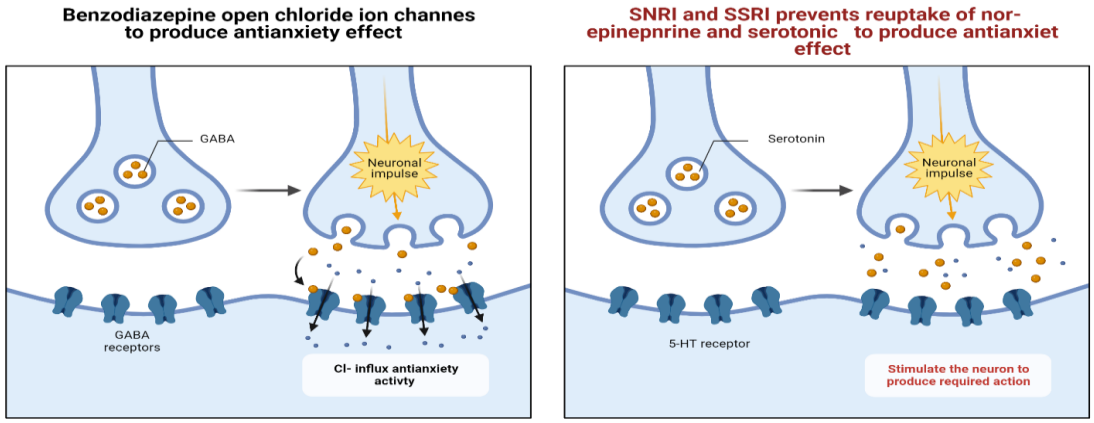


Figure Mechanism of anxiolytic drugs

2. Methodology

By using phrases like "folk use," "anxiolytic," "antianxiety phytoconstituents," "phytotherapy," "medicinal plants," and "sedative mechanism," this study hopes to collect several research papers and reviews on the subject. The most up-to-date information on phytoconstituents that reduce anxiety was gathered through qualitative and quantitative assessments of data from PubMed, Science Direct, direct journal contents, clincialtrial.gov, plantlist.org, and scholarly books and journal articles found in libraries. The review's authors carefully sifted through more than 280 publications published in the last 66 years, and only those papers directly relevant to the review's stated goal were included. Our criteria encompass conventional and alternative treatments for anxiety disorders, focusing on the therapeutic potential of plant compounds known as phytoconstituents. Studies that looked at the anxiolytic properties of phytoconstituents in vitro or in vivo, or those used synthetically produced active compounds having an anticonvulsant effect, were omitted. Using this technology, scientists have isolated 40 potent ingredients from medicinal plants used for centuries in alternative anxiety treatments. All medicinal plants' most up-to-date scientific names were gleaned from Plantlist.org. Finally, clincialtrial.gov was searched for reports of ongoing trials of phytoconstituents in the clinical study and finished trials of phytoconstituents to assess their efficacy and safety in treating anxiety.

3. Results

In Table 1, find an index of phytoconstituents, organized alphabetically by botanical category. Anxiety-relieving herbs used in traditional medicine are described in Column 3. After that, we looked for studies that mentioned the phytoconstituents' antianxiety effects in the literature. Animal studies have been conducted on every phytoconstituent, but in vitro studies have been scarce. Information on anticonvulsants was included. However, it came from many different studies. The effects and potential modes of action of the phytoconstituents for which pharmacological evidence was available are summarized in the next section. The recommended consumption order of the various phytoconstituents is provided in Table 1. In animal models, each phytoconstituents listed in Table 1 has demonstrated antianxiety activity and has shown promise as a therapy for different types of seizures. Twenty-eight of the forty phytoconstituents were shown to be helpful against anxiety in the screening models used for this purpose when applied to traditional medicine. These drugs improve gamma-aminobutyric acid-mediated inhibition of nerve cells. Effectiveness is due to the medications' modulation of ionotropic GABA (A) receptors, which are highly represented in the central nervous system. This article identified several phytoconstituents as having a common biological target, and that target was the GABAergic system. Alkaloids and flavonoids followed shortly after. There is a dire paucity of clinical research on the effectiveness of phytoconstituents with antianxiety potential. As a result, the data in Table 2 illustrates the therapeutic potential of several phytoconstituents.

Table 1: Summary of anxiolytic phytoconstituents with their proposed biological target

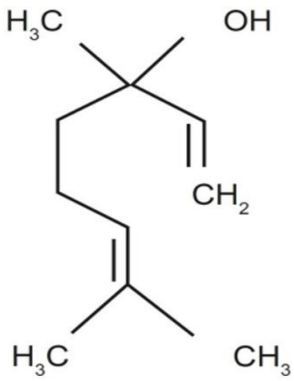
Phytoconstituents	*Medicinal plants*	*Plant part related to anxiety*	*Experimental model*	*Therapeutic target/Mode of action*	*References*
Linalool	Ocimumbasilicum	Anxiolytic activity	Odor-induced anxiolytic effects in mice	γ-aminobutyric acid (GABA)ergic transmission via benzodiazepine (BDZ)-responsive GABAA receptors	(15, 16)
Hypericin	Hypericum perforatum	Total extract affects exploratory behavior and exerts anxiolytic effects	Light–Dark model of anxiety, locomotor behavior	Effects on GABA-activated chloride currents	(17)

Cardiospermin	Cardiospermum halicacabum	Root extracts possess antianxiety activity	Elevated plus-maze model of anxiety, light-dark model of anxiety, open field model of anxiety	Target GABA receptor	(18)
Chrysin	Passiflora incarnata	Methanolic extract exhibit significant anxiolytic activity	Elevated plus maze in mice	Antianxiety activity by acting on GABA A receptors	(19-22)
Cinnamic acid	Cinnamomum cassia	Ethanolic extract of stem barks of C. cassia possesses anxiolytic activity	Elevated plus maze test, Locomotor activity test, Horizontal wire test	Involvement of 5-HT1A and GABAA receptors in the anxiolytic-like effects	(23-26)
P-coumaric acid	Panax ginseng	Korean Red Ginseng from the roots of Panax ginseng for anxiolytic acid	Elevated plus maze (EPM) and marble burying tests (MBT)	Activates the GABA-A	(27, 28)
Caffeic acid	Coffea arabica	Extract Coffee arabica leaves	Automatic hole board, Tail Suspension Test, and memory-Maze test	Activates the GABA-A	(29, 30)
Ferulic acid	Zea mays	Ethanol extract of Zea mays husk	Elevated plus maze model	Mitigation of NMDA receptor pathway	(31, 32)
Sinapic acid	Camelina sativa	Seed Extract of Camelina sativa	Y maze test and elevated plus maze test	GABAA-benzodiazepine receptor – Cl – channel complex	(33, 34)
Sanjoinine A	ZizyphiSpinosi Semen	methanol extract of the plant	Elevated plus maze model	Modification of GABA-ergic systems	(35, 36)
Obovatol	Magnolia obovata	leaves of plant	Y maze test and elevated plus maze test	Acting on GABA-benzodiazepine receptor	(37) Seo et al., 2007
Magnolol	Magnolia	Bark extract of	Elevated plus	Interaction	

	officinalis	M. officinalis	maze model	with the γ-aminobutyric acid receptor GABA	(38)
Honokiol	Magnolia officinalis	Bark extract of M. officinalis	Elevated plus maze model	Interaction with the γ-aminobutyric acid receptor GABA	(38-40)
Quercetin	Tilia americana	Inflorescence and leaves	Y maze test	GABAergic and serotonergic systems	(41)
Kaempferol	Apocynumvenetum	Leaf extract	Elevated plus maze model	Antianxiety activity by acting on GABA A receptors	(42, 43)
Apigenin	Turneraaphrodisiaca	leaves, stems, flowers and fruits parts	Elevated plus maze model	Antianxiety activity by acting on GABA A receptors	(44-45)
Ginkgolide B	Ginkgo biloba	G. biloba extract	Elevated plus maze model	Benzodiazepine like activity	(46-48)
Ginkgetin	Ginkgo biloba	G. biloba leaves	Elevated plus maze model	Antianxiety activity by acting on GABA A receptors	(49)
Sciadopitysin	Ginkgo biloba	G. biloba leaves	Y maze test and elevated plus maze test	Antianxiety activity by acting on GABA A receptors	(50, 51)

3.1 Antianxiety activity of phytoconstituents

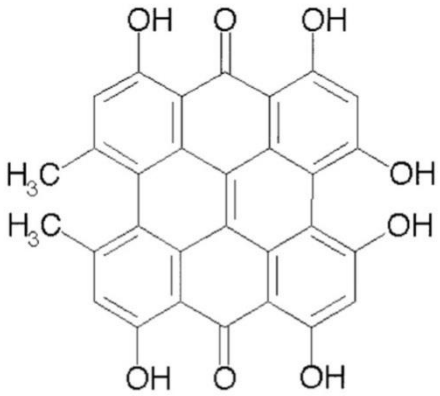
3.1.1 Linalool



3,7-Dimethylocta-1,6-dien-3-ol

Terpene alcohol linalool has a floral and spicy scent. It can be found in around 200 plant species, including citrus fruits and lavender. Analyses of the psychoactive effects of linalool in mice showed that it possessed hypnotic and hypothermic qualities, as well as protection against convulsions generated by pentylenetetrazol, picrotoxin, quinolinic acid, and electroshock, all of which depended on the dose. Linalool is a monoterpene that is a prominent component of the essential oils of many aromatic plant species, including those that have long been used medicinally to induce sleep. The release of glutamate in response to potassium is suppressed by linalool but not under normal conditions. It blocks the activity of glutamate receptors in the brain's cortical membranes and has a similar effect as a non-competitive antagonist of these receptors (52-56).

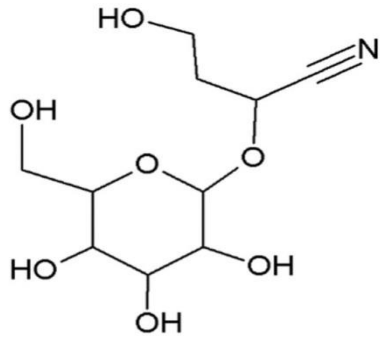
3.1.2 Hypericin



1,3,4,6,8,13-Hexahydroxy-10,11-dimethylphenanthro[1,10,9,8-opqra]perylene-7,14-dione

Antibiotic, antiviral, and non-specific kinase inhibiting properties of hypericin have all been postulated for it. Hypericin can potentially increase dopamine by inhibiting dopamine hydroxylase, but it may have the opposite impact on norepinephrine and epinephrine. Scientists believed that monoamine oxidase inhibition was responsible for hypericin's antidepressant pharmacological action for a while. Current ideas suggest that antidepressants achieve their effects by preventing the brain's reuptake of certain neurotransmitters. Similarly, hypericin is being studied as a possible therapeutic medication in photodynamic treatment, in which a biochemical is absorbed by an organism and subsequently activated by a specific wavelength of light from lamps or lasers.

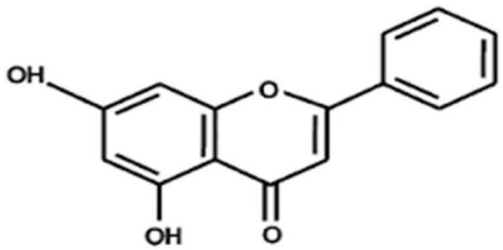
3.1.3 Cardiospermin



2S)-3-(hydroxymethyl)-2-[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybut-3-enenitrile

Traditionally, people have taken the roots of the plant Cardiospermum halicacabum to treat epilepsy and anxiousness. In this study, we tested the calming effects of an ethanolic root extract on anxious rats using the elevated plus-maze (EPM) and the light-dark transition model. Mice were split into two groups: one received diazepam (1mg/kg) orally, while the other received a vehicle (4.0% gum acacia) in the same volume. Extract of C. sativus contained the bioactive component cardiospermin. The anxiety-busting properties of halicacabum have been scientifically confirmed. Moreover, C. halicacabum showed numerous pharmacological effects linked to inflammation, arthritis, diabetes, anxiety, ulcers, apoptosis, disinfection, diarrhea, oxidation, liver and kidney protection, and antioxidant activity.

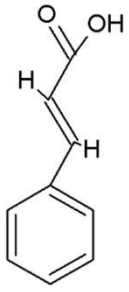
3.1.4 Chrysin



5,7-Dihydroxy-2-phenyl-4H-1-benzopyran-4-one

Whether or not Passiflora incarnata genuinely helps with anxiety is not known. To investigate whether or not chrysin, an extract from the Passiflora plant, might alleviate anxiety, we examined its effects on the GABA(A) receptor and the benzodiazepine receptor in rats. This research aimed to determine if chrysin inhibits anxiety in rats via binding to the GABA(A) receptor. The EPM measured the behavioral effects of anxiolysis, while the catecholamine and corticosterone tests measured neurohormonal effects. For example, in the elevated plus-maze test of anxiety, both diazepam (DZ, 0.3-0.6 mg/kg) and chrysin (1 mg/kg) were reported to exhibit anxiolytic effects by increasing the number of entry into the open arms and the amount of time spent on the open arms. Chysin's negative effects on the elevated plus-maze were mitigated by pretreatment with the specific BDZ receptor antagonist Ro 15-1788 (3 mg/kg).

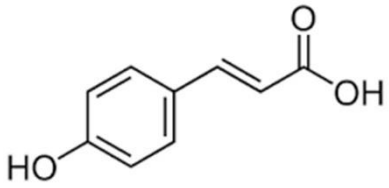
3.1.5 Cinnamic acid



(E)-3-phenyl prop-2-enoic acid

Because of the growing body of data implicating neuronal pro-inflammatory mediators and oxidative stress in the etiology and development of depression, various therapeutic approaches have been experimentally explored to improve the standard of care for depressive disorders. Aromatic acids that have been hydroxylated and methoxylated have been proven to have neuroprotective effects, which is a highly promising finding. Animal studies have examined the antidepressant effects of cinnamic acids like p-coumaric acid, caffeic acid, and ferulic acid.These last three substances are phenolic acids. The FST includes drowning mice or rats in a beaker of water. An ingredient has antidepressant potential if it decreases or postpones the animals' first attempts to escape (dynamic behavior) and increases the frequency and duration of time they float motionlessly (passive behavior).

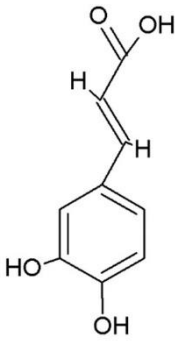
3.1.6 P-coumaric acid



(2E)-3-(4-Hydroxyphenyl)prop-2-enoic acid

The increased incidence of mild to moderate anxiety disorders has a high monetary and human toll in Western societies. Consumers increasingly value non-pharmaceutical, all-natural approaches to managing the stress and anxiety that come with daily life. To test its anxiolytic effects in vivo, researchers used the raised plus paradigm and found that p-coumaric acid, when orally administered to animals, produced results on par with those seen with oral diazepam. Plants contain both free and conjugated forms of the phenolic acid p-coumaric acid, commonly known as 4-hydroxycinnamic acid. It has many beneficial effects in plants, including being a precursor to other phenolic compounds, having relatively low toxicity to mice (LD50 = 2850 mg kg(-1), and having an LD50 of 2850 mg kg(-1)). P-coumaric acid conjugates have received significant attention in recent years due to their bioactivities, and with good reason.

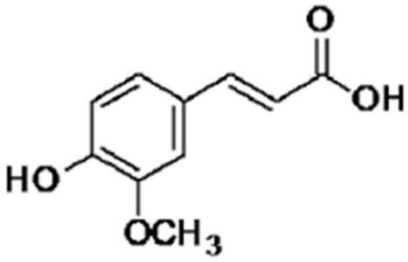
3.1.7 Caffeic acid



(E)-3-(3,4-dihydroxy phenyl)prop-2-enoic acid

The antidepressant-like effects of reserpine were strengthened by EHFAC, which somewhat reduced the akinesia caused by the drug. Pretreatment with EHFAC and CA did not affect the latency to the first seizure or the severity of oxotremorine-induced tremors in mice given a sub-convulsive dose of PTZ. Our study aimed to determine whether caffeic acid's antidepressant and anxiolytic-like effects are mediated via the alpha1A-adrenoceptor system. Mice rendered immobile by forced swimming or frozen by conditioned fear stress recovered more quickly after being given caffeic acid. Somewhat reducing the effects of caffeic acid were antagonists for alpha1- and alpha1A-adrenoceptors. The binding of [3H] prazosin to alpha1A-adrenoceptor in mouse cortical membranes was unaffected by caffeic acid. These data suggest that caffeic acid's depressive and anxiolytic-like effects are due, at least in part, to its indirect modulation of the alpha1A-adrenoceptor system.

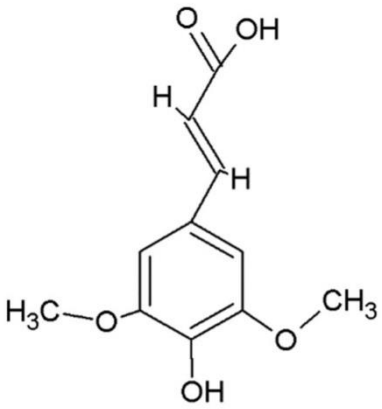
3.1.8 Ferulic acid (FA)



(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid

FA, also known as 4-hydroxy-3-methoxy cinnamic acid (CQA5), is a naturally occurring polyphenol in many foods. The 3,5-diCQA6 and CQA derivatives present in purple sweet potato extract7 have been shown to have neuroprotective properties, as we demonstrated earlier. Becauserosmarinic acid (RA), another CQA derivative, showed antidepressant activity8, 9; it is fair to suppose that FA, another CQA derivative, may also have antidepressant-like effects. The authors of this study utilized the light-dark test to assess the anxiolytic effects of ferulic acid and its possible mechanism of action, which is essential because many antidepressants are also helpful in treating anxiety. After administering ferulic acid and positive control to rats, the anxiolytic impact was determined using the light-dark preference test (clonazepam or fluoxetine). The clonazepam and fluoxetine groups benefited from ferulic acid's apparent compartment time-improving effects at the 250 and 500 mg/L levels.

3.1.9 Sinapicacid

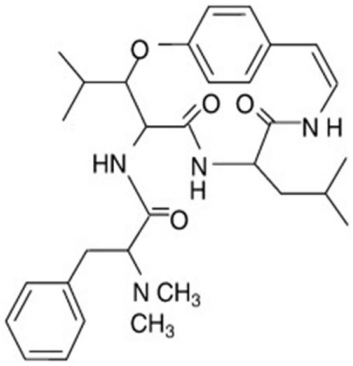


3,5-Dimethoxy-4-hydroxycinnamic acid

Several plants and entire grains contain the phenylpropanoid molecule known as sinapic acid. Unfortunately, the pharmacological characteristics of sinapic acid are mostly

unknown, except for its antioxidant effects. In order to determine if sinapic acid has anxiolytic-like properties, the current study utilized the elevated plus-maze (EPM) and hole-board test. Diazepam (1 mg/kg, i.p.) was given to some mice, while the same volume of vehicle (10% Tween 80 solution) was given to others. Since sinapic acid is a plant chemical in many different foods, it is easy to obtain. This includes fruits, vegetables, grains, oilseeds, spices, and even some medicinal plants. Plants in the Brassicaceae family typically include compounds made from sinapic acid. Sinapic acid has been demonstrated to have a sedative effect on anxious people, adding to its long list of advantages (such as its antioxidant, antibacterial, anti-inflammatory, anti-cancer, and antianxiety effects). Decarboxylation of sinapic acid generates 4-vinylsyringol, a powerful antioxidant and antimutagenic agent that inhibits carcinogenesis and cytokine production.

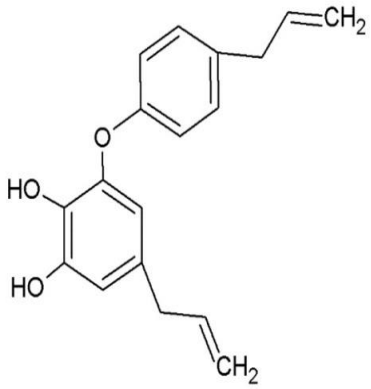
3.1.10 Sanjoinine A



(2*S*)-2-(dimethylamino)-*N*-[(3*S*,4*S*,7*S*,11*R*)-11-hydroxy-7-(2-methylpropyl)-5,8-dioxo-3-propan-2-yl-2-oxa-6,9-diazabicyclo[10.2.2]hexadeca-1(14),12,15-trien-4-yl]-3-phenylpropanamide

The anxiolytic effects of one of the principal alkaloid components in ZizyphiSpinosi Semen (ZSS) were compared to those of the reference anxiolytic diazepam. Among the neolignans found in Magnolia officinalis, 4-O-methylhonokiol was found to have anxiolytic-like effects in experimental paradigms incorporating anxiety, and these effects were comparable to those of the commonly used anxiolytic pharmaceutical, diazepam. Animals were given 4-O-methylhonokiol (0.1, 0.2, and 0.5 mg/kg, p.o.) or therapy for seven days (0.5 mg/kg in drinking water) spent more time in the elevated plus-maze test and made more entries into the open arms.

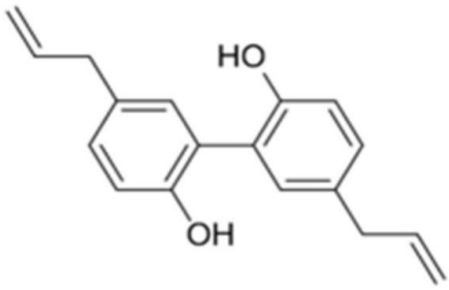
3.1.11 Obovatol



5-prop-2-enyl-3-(4-prop-2-enylphenoxy)benzene-1,2-diol 1,2-Benzenediol, 5-(2-propenyl)-3-(4-(2-propenyl)phenoxy)- 5-allyl-3-(4-allylphenoxy)benzene-1,2-diol

Notobovatol's anxiolytic effects on mice were evaluated using the elevated plus maze and the automated hole board. Results from an elevated plus-maze test showed that obovatol significantly increased the number of trials in which subjects remained in the test's open arm and the amount of time they remained in the arm compared to saline. Ovatol (0.2, 0.5, and 1.0 mg/kg) also induced similar increases in head-dipping, suggesting anxiolytic-like effects. This effect was similar to the typical dose of the diazepam antianxiety drug (1.0 mg/kg). Anxiolytics are drugs used to treat anxiety, and their primary pharmacological target is the gamma-aminobutyric acid (GABA) system. Anxiety disorders have been linked to low levels of the inhibitory neurotransmitter GABA. Several psychiatric problems, such as anxiety, insomnia, and epilepsy, have been linked to GABAergic system deficiencies (57-59).

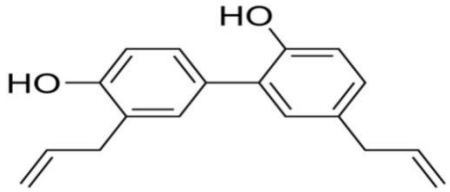
3.1.12 Magnolol



5,5′-Di(prop-2-en-1-yl)[1,1′-biphenyl]-2,2′-diol

It is estimated that up to 25% of the population in the United States will experience an anxiety disorder at some point in their lives. Interest in the potential anxiolytic advantages of natural, plant-derived supplements has increased, but benzodiazepines and other prescription medicines remain the clinical standard of care. About 40% of American adults have tried CAM, per a 2007 survey by the National Center for Complementary and Alternative Medicine. Anxiety/stress and insomnia, two of the top 10 disorders experienced by adults and children, were effectively treated by CAM in this survey. Binding to and favorable modification of GABAA receptors is a way via which magnolol and honokiol may alter behavior. Medications for anxiety, insomnia, and epilepsy may all work through the exact mechanism.

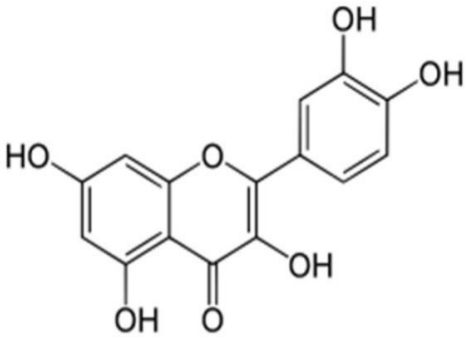
3.1.13Honokiol



3′,5-Di(prop-2-en-1-yl)[1,1′-biphenyl]-2,4′-diol

Honokiol, a neolignane derivative of Magnolia bark, is thought to have major depressive effect and, at much lower concentrations, anxiolytic efficacy. Additionally, flumazenil and bicuculline inhibited the anxiolytic effects of diazepam (1 mg/kg). In contrast, diazepam antagonized CCK-4's actions, and the combination of diazepam and coffee increased those effects. Based on these results, honokiol appears to selectively have an anxiolytic effect, in contrast to diazepam, which is more likely to cause motor dysfunction, sleepiness, or disinhibition. The medicine's synergistic effects also proved that honokiol's anxiolytic activity is exerted somewhat differently than diazepam's. Using the elevated plus-maze, activity, and traction tests, researchers found that honokiol, a neolignane derivative derived from Magnolia bark, significantly reduced anxiety in mice after seven days of administration at 0.2 mg/kg and higher dosages. While 0.2 mg/kg of honokiol was beneficial in treating anxiety, 1 mg/kg of diazepam was more so and led to muscular relaxation (60-62).

3.1.14Quercetin

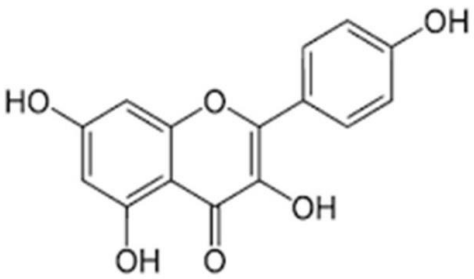


2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one

Tilia species are known for their sedative properties, making them popular among traditional medicine practitioners worldwide. In addition, Tilia americana var. Although we know little about its flavonoid composition, Mexicana is a hybrid of two Mexican Tilia species. Here, we evaluated the flavonoid content and anxiolytic-like reactivity of Tilia inflorescences collected in Mexico from three different regions. Flavonoids have been shown in numerous investigations to increase GABA receptor activation. Quercetin and its glycoside cousin rutin have been shown to reduce anxiety and prevent seizures.

These flavanoids were also found to be more efficacious when taken orally. Potentially helpful in treating neurological disorders, these metabolites are worth further investigation. Anxiety symptoms include restlessness, tense muscles, trouble focusing, irritability, and an inability to fall or remain asleep. Hyperactivation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system causes the physiological symptoms of anxiety to manifest. These symptoms include shallow breathing, sweating, nausea, rapid heartbeat, and elevated blood pressure.

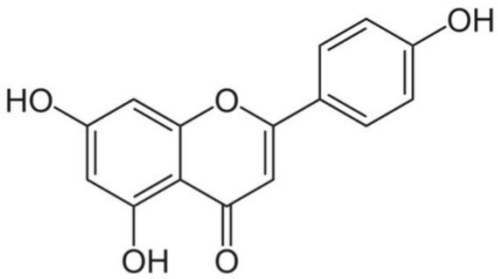
3..1.15 Kaempferol



3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one

Recent scientific research has revealed that several plants traditionally used for medicinal purposes have pharmacological qualities that may be useful in treating anxiety disorders. Melilotus officinalis (Fabaceae) is a plant whose aerial portions have been used medicinally for centuries to treat convulsions and sleeplessness and as a nervine tonic. Despite its long history of use in nervous system disorders, no comprehensive phytochemical and pharmacological research has been undertaken on this promising herb. The elevated plus maze (EPM) was utilized as a model in mice to determine if an aqueous extract of Apocynumvenetum L. could reduce anxiety (Apocynaceae). Significantly more time was spent on the open arms of the EPM when AV extract was administered, indicating probable anxiolytic-like activity across two dose ranges (22.5-30 and 100-125 mg/kg p.o.) (21).

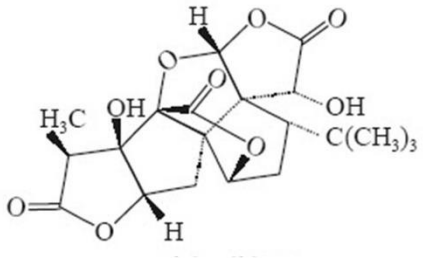
3.1.16 Apigenin



5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

The aphrodisiac Turnera. Traditional uses of Ward (Turneraceae) for treating anxiety neurosis and as an aphrodisiac lack scientific support. This study aimed to identify the chemical(s) in T. aphrodisiaca responsible for the plant's therapeutic properties. Extracts of T. repens in methanol were used to isolate the anxiety-reducing component apigenin. Methods for bioactivity-guided fractionation9 of the aphrodisiaca plant's aerial parts. The current work aimed to standardize the aphrodisiaca aerial plant according to its bioactive marker by using an HPTLC densitometric approach for quantifying apigenin in T. leaves, stems, flowers, and fruits.

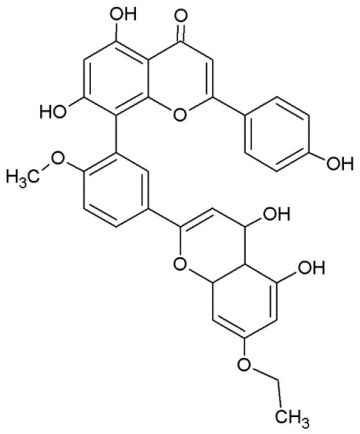
Ginkgolide B



(1*R*,3*R*,6*R*,7*S*,8*S*,10*R*,11*R*,12*R*,13*S*,16*S*,17*R*)-8-*tert*-butyl-6,12,17-trihydroxy-16-methyl-2,4,14,19-tetraoxahexacyclo[8.7.2.0]nonadecane-5,15,18-trione

Ginkgo biloba contains ginkgolides, which are physiologically active terpenic lactones. Biosynthesis from geranylgeranyl pyrophosphate produces these 20-carbon diterpenoids. In the central nervous system (CNS), ginkgolide B acts as a natural regulator of glutamate function according to its origins as an extract from the leaves of the Ginkgo biloba tree. (63-65).

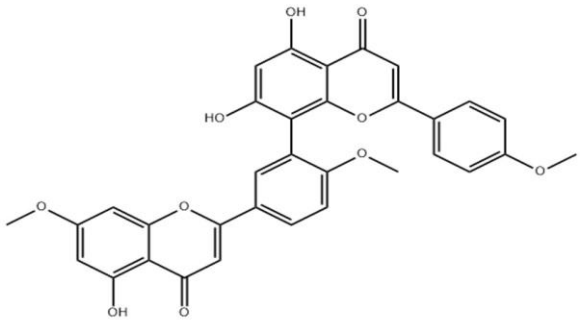
Ginkgetin



5,7-dihydroxy-8-[5-(5-hydroxy-7-methoxy-4-oxochromen-2-yl)-2-methoxyphenyl]-2-(4-hydroxyphenyl)chromen-4-one

Ginkgetin is a biflavonoid that is derived from amentoflavone as a 7,4'-dimethyl ether—removed from Ginkgo biloba. Ginkgetin is a naturally occurring, non-toxic biflavone that has been studied for its preventive effects against cancer, inflammation, microorganisms, adipose tissue, and nerve cells. Inhibiting the cell cycle, inducing apoptosis, promoting autophagy, and targeting many aberrant signaling pathways like JAK/STAT and MAPKs are ways GK helps fight cancer progression. GK exhibits substantial neuroprotection against oxidative stress-induced cell death by, among other things, inhibiting cerebral micro-hemorrhage, minimizing neurologic impairments, and reducing neuronal apoptosis. GK also has antimicrobial, antiviral, antibacterial, leishmanicidal, and plasmodial effects. (66-68).

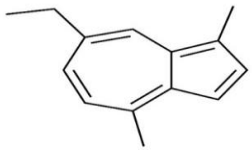
Sciadopitysin



5,7-dihydroxy-8-[5-(5-hydroxy-7-methoxy-4-oxochromen-2-yl)-2-methoxyphenyl]-2-(4-methoxyphenyl)chromen-4-one

The biflavonoidsciadopitysin is derived from amentoflavone and is a 7, 4', 4"'-trimethyl ether. It prevents platelets from sticking together and helps keep bones strong (Šamec et al., 2022; He et al., 2021). It consists of two flavonoids, two hydroxyflavones, two methoxyflavones, and a ring structure. It shares some properties with amentoflavones. Sciadopitysin is a biflavonoid initially isolated from G. biloba and has numerous biological functions. Dementia, depression, and anxiety disorders, among others, have been treated with plant extracts as medicines by people of many various cultural backgrounds for thousands of years. Millions of individuals worldwide have used extracts from the tree Ginkgo biloba (order Gingophyta). Extracts of the tree Ginkgo biloba have been studied as a possible herbal remedy for improving mental performance. (69, 70).

Chamazulene

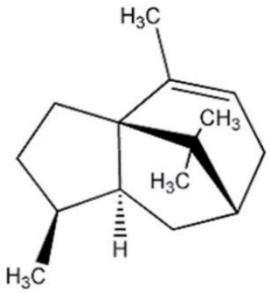


7-ethyl-1,4-dimethylazulene

Extracts of chamomile include a compound called chamazulene. Chamazulene may boost the anti-inflammatory effects of chamomile extracts by inhibiting the formation of leukotrienes and engaging in additional antioxidative functions (Safayhi et al., 1994; Srivastava et al., 2009; Flemming et al., 2015; Fabian et al., 2011; Rahman et al., 2022; Mitoshi et al., 2012; Albrecht et al., 2014). Long-

term use of Chamomile (Matricariarecutita) extracts significantly reduced the moderate to severe anxiety symptoms associated with generalized anxiety disorder. Many people use chamomile because it helps them relax and fall asleep. It has been hypothesized that chamomile's beneficial benefits on mood and anxiety are due to its ability to elevate levels of the feel-good neurotransmitters serotonin, dopamine, and noradrenaline in the brain (71).

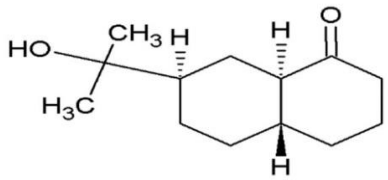
Alpha-patchoulenese



4,10,11,11-tetramethyltricyclo[5.3.1.0]undec-9-ene

Origanum sipyleum and Asarum yakusimense both contain the natural compound alpha-patchoulene. Origanum is a genus of herbaceous perennials and subshrubs in the family Lamiaceae. It is endemic to open or mountainous regions of Europe, North Africa, and much temperate Asia.

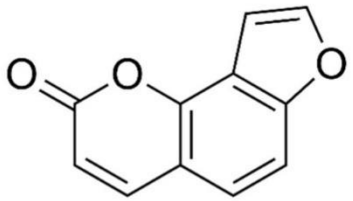
Beta-eudesemol



2-[(2R,4aR,8aS)-4a-methyl-8-methylidene-1,2,3,4,5,6,7,8a-octahydronaphthalen-2-yl]propan-2-ol

Atractylodes (72), Teucrium (73), and Anaxagorea (74) are all examples of medicinal plants that contain the oxygenated sesquiterpene beta-eudesmol, which also accumulates in specific hop cultivars (75) and Eucalyptus (74, 76). Anti-angiogenic activity, anti-tumor activity, blocking the action of succinylcholine on acetylcholine-activated channel activity, and activation of transient receptor potential channels have all been reported for Eudesmol in a mammalian model. However, the applicability of these effects to humans has not been well studied. (77-79). Recently, it was discovered that rats' adrenal efferent sympathetic nervous system could be suppressed after receiving an oral dosage of Eudesmol, which altered autonomic nerve activity (80). Clinical investigations of Eudesmol's effects on autonomic nerve activity in response to stressors have been inconclusive, and it remains uncertain whether this chemical has any value in humans.

Angelicin

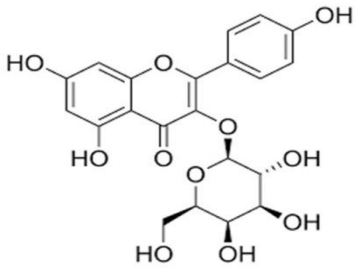


furo[2,3-h]chromen-2-one

A. archangelica

Angular furanocoumarins are a class of naturally occurring chemical compounds derived from angelicin (81). It is a benzapyra-2-one with a furan moiety attached to the 7,8 positions. For example, Angelica archangelica, which belongs to Apiaceae and Fabaceae, is a good source of angelicin (82-85). The furocoumarin family, of which angelicin is a part, includes the well-known phototherapeutic agent psoralen (86). While the furocoumarins as a class have been the research topic since the 1950s, angelicin has only started to receive the attention it deserves. Angelicin is more effective than psoralen at blocking tubulin polymerization and has been shown to have anti-cancer effects against a range of cell lines by inhibiting both intrinsic and extrinsic apoptotic pathways. (87-89). Angelicin's ability to inhibit nuclear factor-kappaB activation has also been linked to its anti-inflammatory effects in pulmonary and neurological illnesses caused by inflammation. (90, 57).

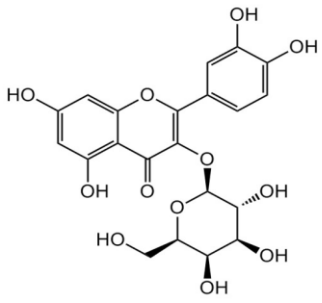
Trifolin



5,7-dihydroxy-2-(4-hydroxyphenyl)-3-[(2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one

A molecule of chemical substance that is known as trifolin. To be more exact, it is the type of kaempferol that is known as 3-galactoside. It can be found in certain species of the genus Euphorbia. Euphorbia hirta has been linked to a very diverse array of biological processes and impacts (Eh). Antidiarrheal, spasmolytic and antiamoebic actions have been shown to be produced in vitro using preparations that are manufactured in accordance with conventional procedures. In its native Africa and Australia, this herb has been used to cure a wide variety of diseases and conditions, including high blood pressure, edoema, and malaria, among others. It has been shown that extracts of Euphorbia hirta Linn possess central analgesic, antipyretic, and anti-inflammatory activity in addition to its central depressant, sedative, and anxiolytic effects. The ability of the medicine to alleviate anxious behaviour in mice was demonstrated with the use of the two-chamber, staircase, and light-dark choice tests (91).

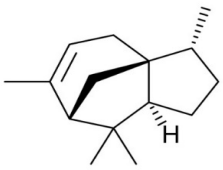
Hyperoside



2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one

The active chemical, hyperoside, is found in hydrocotyle plants. The flavonol glycoside hyperoside (or quercetin-3-O-galactoside) is abundant in Hypericum and Crataegus plants and fruits. Its potent antithrombotic, anti-inflammatory, hepatoprotective, anti-diabetic, and antioxidant activities have been demonstrated in a wide range of experimental animals. The effects of the genus Hydrocotyle on the central nervous system have been the topic of substantial study, particularly with respect to Hydrocotyle asiatica L. (Centella asiatica (L.) Urb.). There is evidence that the herb centella can improve memory and learning by lowering anxiety and increasing hippocampus-based dendritic development (92).

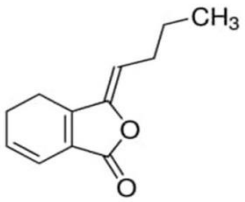
Cedrene



2,6,6,8-tetramethyltricyclo[5.3.1.0]undec-8-ene

Cedrene is a sesquiterpene that can be found in cedarwood oil (Juniperus virginiana). The Juniperus virginiana L. tree is the source of the essential oil known as cedarwood wormwood oil (CWO), which has a long history of usage in the treatment of many medical conditions. There were contradictory findings when it was tested on animal models of anxiety (93).

Ligustilide



(3Z)-3-butylidene-4,5-dihydro-2-benzofuran-1-one

Z-ligustilide, which has been associated to antidepressant effects, is the component of Angelica sinensis (Oliv.) Diels (AS) that is considered to be the active ingredient. Angelica sinensis (Oliv.) Diels (AS) is a plant that is well-known in traditional Chinese medicine and has been used to treat a number ofgynaecological disorders. Several animal models of cerebral ischemia have also been used to demonstrate the neuroprotective benefits of ligustilide, suggesting that it may decrease edoema in the brain, ameliorate neurobehavioral abnormalities, and decrease infarct size in the ischemic area. These findings are supported by the fact that ligustilide has been shown to be effective in protecting neurons from damage (94). In addition, it is thought that ligustilide can prevent nerve damage that is caused by hypoperfusion of the cerebral cortex, can reduce apoptosis in the cortical neurons, and can maintain the structural integrity of the neurons (93).

Conclusion

The phytoconstituents discussed here showed promise as an antianxiety, and they posed less risk than many other pharmaceutical options. Anxiolytics that are both safe and efficacious may be abundant among medicinal plants. However, a comprehensive study on the toxicological profile of the phytoconstituents is necessary to determine whether they pose any health risks. Scant data supports the medicinal efficacy of these phytoconstituents in individuals with anxiety, but few plants have been the subject of many clinical investigations. Therefore, the screening data reported here strongly support the development of novel anxiolytic medications derived from medicinal plants and their future use as an alternative therapy option.

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