

HERBAL DRUGS IN MIRROR OF ANXIETY DISORDER -A REVIEW

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ABSTRACT

Traditional Medicines derived from medicinal plants are used by about 60% of the world's population. This review focuses on Herbal drugs used in the treatment of Anxiety disorder. Anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD), are the most prevalent behavioral disorders in the United States, affecting 17.2% of the population. The use of herbal supplements to treat anxiety has been increasing and the mechanisms of action of several are being elucidated. A list of medicinal plants with proven antianxiety effects used in treatment of Anxiety is compiled. These include, *Citrus paradise*, *Cirsium rivulare*, *Drymaria cordata*, *Colocasia esculenta*, *Souroubea sympetala*, *Rollinia mucosa*, *Aethusa cynapium*, *Uncaria rhynchophylla*, *Cinnamomum cassia*, *Gastrodia elata*, *Apocynum venetum*, *Turnera aphrodisiaca*, *Scutellaria lateriflora*, *Valeriana officinalis*, *Galphimia glauca* etc.

KEY WORDS: Herbal Drugs, Antianxiety, Anxiety

INTRODUCTION

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter^[1]. The current review focuses on herbal drug used in the treatment of anxiety disorders, among the most common mental disorders besides depressive disorders with approximately one-eighth of the world population affected at some point in their life^[2]. Anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD), are the most prevalent behavioral

disorders in the United States, affecting 17.2% of the population.

MEDICINAL PLANTS WITH ANTIANXIETY EFFECTS:

Citrus paradisi var. *star ruby* (Grapefruit):

Citrus paradisi has been used traditionally to reduce stress and anxiety. The anti-anxiety activity of various extracts viz petroleum ether, chloroform, methanol and water, of the leaves of *Citrus paradisi* var. *star ruby* using elevated plus maze (EPM) model in Swiss albino mice were evaluated. Results show that methanol extract at the dose of 100mg/kg of the leaves of *Citrus paradisi* var. *star ruby* markedly increased the average time spent in the open arms of the EPM^[3].

***Cirsium rivulare* (Ornamental thistle):**

Cirsium rivulare (Asteraceae) is a herbaceous perennial plant occurring in Central Europe. It has been traditionally used in Polish folk medicine to treat anxiety. Methanolic extracts from flowers and leaves of *Cirsium rivulare* containing flavonoid compounds linarin, pectolarin, apigenin, hispidulin, their glycosides and a newly isolated compound isokaemferide 7-O-(6"-methylglucuronide) were studied for anxiolytic and pro-cognitive properties. The flavonoids from *Cirsium rivulare* leaves possess anxiolytic properties [4].

***Drymaria cordata* (Tropical chickweed):**

Drymaria cordata hydroethanolic extract (DCHE) at 25, 50 and 100 mg/kg (p.o.) was administered to study anxiolytic effect. Different models for anxiolytic activity viz. Hole board, Open field, Elevated plus maze, Light/dark exploration model were used. The presence of phytochemicals viz. triterpenes, diterpenes, steroids and tannins might contribute to its anxiolytic activity [5].

***Colocasia esculenta* (Arvi):**

Colocasia esculenta Linn. (Araceae), commonly known as elephant ear (English), possesses diverse pharmacological activities. The neuropharmacological activities of hydroalcoholic extract of leaves of *Colocasia esculenta* were evaluated. The anxiolytic activity of HECE (100, 200, and 400 mg/kg) per os (p.o.) was characterized by increased time spent and number of entries in open arms in the EPM paradigm as compared to control group ($p < 0.001$). The presence of flavonoids, beta-sitosterol, and steroids

might contribute to its anxiolytic activity [6].

***Souroubea sympetala*:**

Souroubea sympetala Gilg (Marcgraviaceae) is a traditional anti-anxiety plant. SCE (supercritical carbon dioxide extraction) can be used to generate a betulinic acid-enriched extract with significant anxiolysis in vivo [7].

***Rollinia mucosa* (Wild sugar apple):**

Rollinia mucosa (Jacq.) Baill. (Annonaceae) extract induced anxiolytic-like actions similar to those induced by diazepam in the avoidance exploratory behavior paradigm. Its significant activity was shown at doses from 1.62 to 6.25 mg/kg [8].

***Aethusa cynapium* (Dog Poison):**

Aethusa cynapium L. (Apiaceae) is commonly called Fool's parsley, dog's parsley or lesser hemlock. Bioactivity guided fractionation of the anxiolytic methanol extract of *A. cynapium* has led to the isolation of a novel unsaturated fatty acid. This new fatty acid-trideca-7,9,11-trienoic acid, isolated from *A. cynapium* was found to be responsible for the antianxiety activity of the plant [9].

***Uncaria rhynchophylla*:**

The aqueous extract of roots with stem of *Uncaria rhynchophylla* were characterized for the anxiolytic like effects using the elevated plus maze (EPM) and the hole-board apparatus in rats and mice. Single or repeated treatments of the aqueous extract of *Uncaria rhynchophylla* (200 mg/kg/day, p.o.) for 7 days significantly increased the time-spent and entries into open arms of the EPM, and reduced the

time-spent and entries into the closed arms versus saline controls ($P < 0.05$)^[10].

***Cinnamomum cassia* (Dalchini):**

The anxiolytic-like effects of a 50% EtOH extract of *Cinnamomum cassia* (*C. cassia*) were determined. A single treatment with *C. cassia* (750 mg/kg, p.o.) significantly increased the number of entries into and the time spent in the open arms of the EPM compared with the controls^[11].

***Gastrodia elata*:**

The anxiolytic-like effects of the aqueous extract of the rhizome of *Gastrodia elata* along with its phenolic constituents, 4-hydroxybenzyl alcohol (HA) and 4-hydroxybenzaldehyde (HD), using an elevated plus maze (EPM) in mice were characterized. A single treatment of the aqueous *G. elata* extract significantly increased the percentage of time spent and arm entries into the open arms of the EPM versus the saline controls. Among the phenolic constituents of *G. elata*, HA and HD significantly increased the percentage of time spent and arm entries into the open arms of the EPM versus saline controls ($p < 0.05$)^[12].

***Apocynum venetum* L.:**

O. Grundmann et al. evaluated the anxiolytic activity of an aqueous extract of *Apocynum venetum* L. (Apocynaceae) and bioguided its fractionation using the elevated plus maze (EPM) in mice as a model of anxiety. A single treatment of AV extract markedly increased the percentage time spent on the open arms of the EPM in two distinct concentration ranges of 22.5–30 and 100–125 mg/kg p.o., respectively, indicating a putative anxiolytic-like activity^[13-14].

***Turnera aphrodisiaca* (Damiana):**

Apigenin, a bioactive principle of *Turnera aphrodisiaca* Ward (Turneraceae) was evaluated for antianxiety activity at a dose of 2 mg/kg using well established models of anxiety, the hole board test, light/dark test and mirrored chamber test. Observations confirmed the anxiolytic activity of apigenin. Maximum activity was observed 30 min after the administration of 10 mg/kg dose of apigenin^[15].

***Scutellaria lateriflora* L. (Scullcap):**

The phytochemistry and biological activity of *Scutellaria lateriflora* L. (American skullcap) which has been traditionally used as a sedative and to treat various nervous disorders such as anxiety was studied. The identification and quantification of the flavonoid, baicalin in a 50% EtOH extract (40 mg/g) and its aglycone baicalein in a 95% EtOH extract (33 mg/g), as well as the amino acids GABA in H₂O and EtOH extracts (~1.6 mg/g) and glutamine in a H₂O extract (31 mg/g), was performed using HPLC. These compounds may play a role in anxiolytic activity since baicalin and baicalein are known to bind to the benzodiazepine site of the GABA_A receptor and since GABA is the main inhibitory neurotransmitter^[16].

***Valeriana officinalis* (Tobacco Root):**

Valerian root (*Valeriana officinalis*) is a popular and widely available herbal supplement, primarily used to treat insomnia and anxiety. Neurobiological research has begun to show that the herb, with its active valerenic acid, interacts with the GABA_A-ergic system, a mechanism of action similar to the benzodiazepine drugs. Results showed

that there was a significant reduction in anxious behavior when valerian extract or valerianic acid exposed subjects were compared to the ethanol control group. The evidence supports *Valeriana officinalis* as a potential alternative to the traditional anxiolytics as measured by the elevated plus maze [17].

***Galphimia glauca* (Gold shower):**

An infusion prepared with aerial parts from *Galphimia glauca* has been widely used in Mexican traditional medicine as a remedy for nervous excitement. The anxiolytic like effects of *G. glauca* methanolic extract (standardized on GB content, 8.3 mg/g) were assayed by using the elevated plus-maze, on ICR albino mice. This extract, administered orally, three times (24, 18 and 1 h before the test), and in different doses (125, 250, 500, 1000 and 2000 mg/kg) was able to increase significantly ($p < 0.05$) the number of entries, as well as the time spent in the open arms of the elevated plus-maze, indicating an anxiolytic-like effect [18].

***Morinda citrifolia* (Mulberry):**

Noni (*Morinda citrifolia*) is increasing in worldwide popularity as a food or dietary supplement with versatile health benefits. Noni fruit indicate the presence of competitive ligand(s), which may bind to the GABA_A receptor as an agonist, and thus induce its anxiolytic and sedative effects [19].

***Aniba riparia*:**

Methyl ethers of *N*-(2,6-dihydroxybenzoyl) tyramine (riparin III) isolated from the unripe fruit of *Aniba riparia* was administered intraperitoneally to male mice at single doses of 25 and 50 mg/kg. At the dose of 50 mg/kg, riparin

III increased the number of entries in the open arms of the EPM test as compared with control. Riparin III potentiated the barbiturate-induced sleeping time and presented antidepressant- and anxiolytic-like effects [20].

***Calotropis gigantea*:**

Alcoholic extract of peeled roots of *Calotropis gigantea* R.Br. (Asclepiadaceae) was tested orally in albino rats at the dose level of 250 and 500 mg/kg bodyweight for CNS activity. The extract treated rats spent more time in the open arm of EPM showing its antianxiety activity [21].

***Piper methysticum* G. Forster:**

Kava-Kava, a drug derived from a traditional psychoactive beverage used in the South Pacific, is known for tranquilizing and anxiolytic effects. Extracts made from the roots of the Kava plant (*Piper methysticum* G. Forster) have anxiolytic and mild sedative effects in man. Kava kava extract (120–240 mg/kg po) affected the behaviour measured in the X-maze test, inducing an anxiolytic like behaviour similar to diazepam (15 mg/kg po) [22].

***Passiflora incarnata*:**

The petroleum ether, chloroform, methanol, and water extracts of *Passiflora incarnata* whole plant have been evaluated for their anxiolytic activity using the elevated plus-maze model in mice. The methanol extracts of leaves, stems, flowers, and whole plant exhibited anxiolytic effects at 100, 125, 200 and 300 mg/kg, respectively [23].

Rubus brasiliensis:

Hexanic ethanolic fraction of *Rubus brasiliensis* Martius (Rosaceae), have been evaluated for their anxiolytic activity using the elevated plus-maze model in Wistar rats and Swiss mice. All the doses of the extract, 50, 100 and 150 mg/kg, administered per gavage (vo), 30 min before the behavioural evaluation, induced an anxiolytic effect expressed by: increased number of entries in and time spent in the open arms and percentage of open arm entries; and decreased number of entries and time spent in the closed arms [24-25].

Aloysia polystachya (Griseb.):

Hydro-ethanolic extract obtained from the aerial parts of *Aloysia polystachya* (Verbenaceae) have been evaluated for their anxiolytic activity using the elevated plus-maze model in male mice. The ethanolic extract significantly increased the percentage of both entries (1.0 and 100.0 mg/kg) and the time spent (10.0 and 100.0 mg/kg) into the open arms of the elevated plus maze (EPM) [26].

Passiflora edulis f. flavicarpa:

Ethanolic extract (EE) of the aerial part of *Passiflora edulis* f. *flavicarpa* and its fractions, viz. petrol ether extract (PEE), ethyl acetate extract (EAE), *n*-BuOH extract (BE) and aqueous extract (AE), together with subfractions of BE, viz. BEF-I, BEF-II, BEF-III, BEF-IV and isoorientin, have been evaluated for their anxiolytic activity using the elevated plus-maze model in male mice. Single-dose oral administration of EE (300 mg/kg and 400 mg/kg), BE (125 mg/kg and 200 mg/kg), AE (200 mg/kg and 300 mg/kg), BEF-I (200 mg/kg), BEF-II (200 mg/kg), BEF-III (100 mg/kg), or

isoorientin (20 mg/kg) resulted in anxiolytic like effects [27].

***Coriandrum sativum* L. (Dhania):**

Coriandrum sativum L. has been recommended for relief of anxiety and insomnia in Iranian folk medicine. The anxiolytic effect of aqueous extract (10, 25, 50, 100 mg/kg, i.p.) was examined in male albino mice using elevated plus-maze as an animal model of anxiety. In the elevated plus-maze, aqueous extract at 100 mg/kg showed an anxiolytic effect by increasing the time spent on open arms and the percentage of open arm entries, compared to control group [28].

Cassia siamea:

Cassia siamea, a plant used in Thai traditional medicine, and barakol, its active chemical, were studied on an elevated plus-maze compared with diazepam. An aqueous extract of *C. siamea* (1, 6, and 12 g/kg body wt., orally) produced a small increase in the percentage of the open: total number of arm entries and time, time spent on the end of the open arms, total number of arm entries, and number of rears/min. Barakol at 25 and 50 mg/kg increased the percentage of the open: total number of arm entries and time and number of rears [29].

Scutellariae radix:

Baicalein, one of the active principles of the Chinese herbal drug, Huangqin (*Scutellariae Radix*), and its 7-glucuronide baicalin, have anxiolytic-like effects in a Vogel conflict test. The results showed that both baicalein (10 mg/kg, i.p.) and baicalin (20 mg/kg, i.p.) significantly increased the number of shocks accepted in the Vogel lick-shock conflict paradigm over 9 min, as did a benzodiazepine

receptor agonist, chlordiazepoxide (5.0 mg/kg, i.p.) and a 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (0.5 mg/kg, i.p.)^[30].

Tilia americana var. mexicana:

The ethnomedicinal use of *Tilia americana var. mexicana* inflorescences as sedative and anxiolytic is reinforced by examining inflorescences used by communities of the State of Michoacan, Mexico. A significant attenuation in the anxiety-response in the plus-maze test were observed^[31-32].

Casimiroa edulis:

Anxiolytic-like actions of an aqueous extract of the leaves of *Casimiroa* (Rutaceae) were studied in male Wistar rats in the elevated plus-maze test. Diazepam (Dz) (1.30 mg/kg; $P < 0.05$) and *Casimiroa edulis* (25.0 mg/kg, $P < 0.05$; 35.0 mg/kg, $P < 0.05$) increased open arms exploration (i.e., anxiolytic-like action)^[33].

Ziziphus jujube:

Ethanol extract of *Ziziphus jujube* were evaluated for anxiolytic effect. The SZJE at the dosage 0.5–1.0 g/kg increased the percentage of time-spent and the percentage of arm entries in the open arms of the EPM and decreased the percentage of time-spent and the percentage of arm entries in the closed arms of the EPM^[34].

Piper tuberculatum:

Piplartine (PIP), an amide alkaloid isolated from the roots of *Piper tuberculatum* (Piperaceae), was studied for their anxiolytic effect in the elevated plus maze. Results showed that PIP (50 and 100 mg/kg, i.p.), similarly to

diazepam, significantly increased not only the number of entrances (100% and 66%, respectively) but also the time of permanence in the open arms (104% and 199%, respectively), indicating that PIP presents an anxiolytic activity^[35].

Aloysia polystachya:

Hydroalcoholic extract from leaves of *Aloysia polystachya* (Verbenaceae) were studied for their anxiolytic effect in the elevated plus maze. All doses injected (from 1.56 to 50 mg/kg) increased the exploration of the EPM open arms in a similar way to that of diazepam (1 mg/kg, i.p.). The components of the hydroalcoholic extract of *A. polystachya*, such as thujone and carvone among others, may have anxiolytic and antidepressant-like properties^[36].

Panax quinquefolium:

Xiu-Yan Wei et al. had studied the anxiolytic effect of the saponins from *Anilialea Panax quinquefolium* L. (PQS) in male mice by using a number of experimental paradigms of anxiety and compared with that of the known anxiolytic compound diazepam. Use of the elevated plus-maze test revealed that PQS (50 mg/kg, p.o.) and diazepam (2.5 mg/kg, p.o.) increased the percentage of time and entries spent in open arms^[37].

Scutellaria baicalensis:

Kwok Min Hui et al. evaluated the pharmacological properties of a naturally occurring monoflavonoid, 5,7-dihydroxy-8-methoxyflavone or wogonin obtained from *Scutellaria baicalensis*. Oral administration of wogonin (7.5 to 30 mg/kg) elicited an anxiolytic response that was similar to that elicited by diazepam in the elevated plus-maze; a

dose-dependent increase in open arm entries and time spent in open arms was observed^[38].

Panax ginseng:

The putative anxiolytic activity of the white and red varieties of ginseng, the root of *Panax ginseng*, was investigated in rats and mice by S.K. Bhattacharya et al. White and red varieties of ginseng (20 and 50 mg/kg) showed positive results when tested against several paradigms of experimental anxiety. Both were effective in the open-field and elevated plus-maze tests^[39].

Protium heptaphyllum:

G.F. Aragao et al. examined the anxiolytic and antidepressant effects of the mixture of alpha and beta-amyrin (AMY), pentacyclic triterpenes isolated from the stem bark resin of *Protium heptaphyllum*. In the open-field test, AMY at the doses of 10, 25 and 50 mg/kg, after intraperitoneal or oral administrations, significantly decreased the number of crossings, grooming, and rearing. In the elevated-plus-maze test, AMY increased the time of permanence and the number of entrances in the open arms^[40].

Securidaca longepedunculata:

O.O. Adeyemi et al. investigated the anxiolytic activities of the aqueous root extract of *Securidaca longepedunculata*. The extract (100–400 mg/kg) produced a significant ($P < 0.01$) dose dependent prolongation of the cumulative time spent in the open arms of the elevated plus maze^[41].

Paeonia moutan:

The anxiolytic-like effect of paeonol, a phenolic component from the root bark of *Paeonia moutan*, was studied by Xiao Juan Mi et al. As with 2 mg/kg diazepam, paeonol (at 17.5 mg/kg) increased the percentage of time spent on open arms in the elevated plus maze and increased the time spent in the light area of the light/dark box (at 8.75 and 17.5 mg/kg)^[42].

Celastrus paniculatus (Malkangani):

The *Celastrus* oil, extracted from seeds of *Celastrus paniculatus* tested at 2 dose levels (1 and 1.5 g/kg), exhibited significant anxiolytic activity^[43].

Albizzia lebbbeck (Siras):

Albizzia lebbbeck (Linn.) Benth. of family Mimosaceae is a medium to large sized tree distributed throughout India. The effect of saponin containing, *n*-butanolic fraction (BF), extracted from dried leaves of *Albizzia lebbbeck*, was studied on cognitive behavior and anxiety in albino mice. The anxiolytic activity of BF (0, 10, 25, and 50 mg/kg) was assessed by studying its effect on the duration of occupancy in the closed arm. Animals treated with BF (25 mg/kg) spent more time in the open arm in a dose-dependent manner^[44].

Hypericum perforatum:

H. perforatum is sometimes called **Common St John's wort** family [Clusiaceae](#). The total extract of *H. perforatum* increases the locomotor activity in the open field and exerts anxiolytic activity in the light–dark test, whereas the single components did not show any effect^[45].

Passiflora Coerulea:

The pharmacological effects of 5,7-dihydroxyflavone (chrysin), a naturally occurring monoflavonoid were examined in mice. In the elevated plus-maze test of anxiety, diazepam (DZ, 0.3–0.6 mg/kg) or chrysin (1 mg/kg) induced increases in the number of entries into the open arms and in the time spent on the open arms, consistent with an anxiolytic action of both compounds^[46].

Cecropia glazioui:

Cecropia glazioui Sneth has been used in most Latin American countries as an antihypertensive, cardi tonic, and antiasthmatic folk medicine. Its anxiolytic activity was studied by F.F. Rocha. Swiss mice were treated with AE (0.25–1 g/kg po) acutely (1 h) or repeatedly (24, 7, and 1.5 h before the test). After repeated administration of aqueous extract, the frequency of entries in the open arms of EPM was increased threefold. The AE of *C. glazioui* promotes an anxiolytic-like effect in mice. The active principles responsible for this action are present in the less polar fraction of the extract, the main constituents of which are flavonoids and terpenes, among other compounds^[47].

Salvia reuterana:

M. Rabbani et al. evaluated the anxiolytic effect of hydroalcoholic extract (HE) of *Salvia reuterana* Boiss. in mice. The HE of *Salvia reuterana* (100 mg/kg), increased the percentage of time-spent and the percentage of arm entries in the open arms of the elevated plus-maze^[48].

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