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REVIEW

A systematic updated review of scientifically tested selected plants used for anxiety disorders

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Abstract: The aim of this review is to provide a summary on multidisciplinary scientific information obtained from medicinal plants used worldwide to treat anxiety, focusing on pharmacological and clinical studies. The bibliographical investigation was carried out by consulting five peer-reviewed worldwide database publications for references, and patents. The information gathered on plants with attributed anxiolytic properties are presented as follows: (1) plant extracts with anxiolytic properties evaluated in animal models; (2) plants with clinical trials; (3) identified active compounds in plants that have been assayed in animal models; (4) mechanism of action of anxiolytic plant extracts and compounds; and (5) registered patents for anxiolytic plant preparations. We recorded 112 plant species belonging to 63 botanical families for which the anxiolytic properties had been tested in animal models. Eleven plant species to treat general anxiety disorders as well as eleven species to treat anxiety-associated conditions, had been documented by clinical trials. Thirty-three registers for active compounds belonging to five general types of secondary metabolites had also been recorded. The mechanism of action at the central nervous system level had been determined in 33 plant species, either in their extracts or isolated compounds. Forty-seven patent registrations for plant preparations to be used for the treatment of anxiety were included.

Keywords: anxiolytic compounds, anxiolytic extracts, clinical trials, patents, mechanism of action

Introduction

Anxiety disorders are considered to be a major cause of disability worldwide, and comprise generalized anxiety disorder and other commonly associated conditions, such as phobias, postmenopausal stress, post-traumatic syndrome, somatization and cognitive dysfunction, among others. Patients diagnosed with generalized anxiety disorder exhibit functional impairment as well as a tendency to develop comorbid psychiatric disorders.[1] Effective treatments for this condition are usually focused on eliminating anxiety symptoms and restoring normal function. Conventional anxiolytic drug therapy is considered to be effective, safe, and broad-spectrum in action,[2] but side effects often reduce quality of life, discouraging patients to follow medication protocols. Moreover, many of the medicines used for anxiety include antidepressants, and the use of such agents can cause troubling side effects, ie, cholinergic symptoms, weight gain, sleep disturbances, sexual dysfunction, medication dependence, or gastrointestinal problems.

The use of herbal remedies for the treatment of anxiety is an ancient practice that nowadays has become popular in Western societies. Plant-based medicines rep-

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resent the most popular treatment for an estimated 43% of the worldwide population that use complementary therapy to augment their treatment for anxiety disorders.[3] It is also reported that anxiety disorders has become one of the most common reasons given for trying herbal medicines.[4] However, despite their wide use, there is limited evidence for the efficacy of herbal products when observed in controlled clinical trials. In addition, many natural products are self-prescribed, and there is a lack of scientific evidence to confirm their potential benefits or to point out resulting disadvantages when they are used in combination with patented drugs, or even alone. For example, cases of liver toxicity resulting from use of *Piper methysticum* (kava)[5] or of *Hypericum perforatum*, which can cause drug interactions,[6] have been documented.

A synergistic effect resulting from the presence of various active compounds in one plant acting together to produce a greater effect than that expected from individual substances has been recognized and used in very ancient traditional medicinal practices as in Ayurvedic and Chinese medicine.[7] This approach has now been accepted in modern phytotherapy,[8] and the use of plant multidrug preparations is increasing to treat anxiety, depression, and other cognitive dysfunctions.[9]

Methodology

For this review, the indicated international literature was systematically searched to identify plants with anxiolytic effects that were documented in animal models. In addition, plant species employed in clinical trials to treat generalized anxiety disorder as well as related disorders were reviewed. We also present information about active compounds isolated from plants, and the mechanism of action of plant extracts or compounds. This review also incorporates a worldwide registry of plant patents used in the treatment of anxiety.

PubMed (MedLine), NAPRALERT, and EBSCO were the worldwide databases consulted without a time limit using the terms anxiolytic plant, anxiolytic extracts, anti-anxiety plants, herbal treatment for anxiety, clinical trials, general anxiety disorder, etc. The Espacenet database was used to locate patents from 1967 to the present using the terms plant, herbal, and extract, and cross-linking them with anxiety and anxiolytic terms. This search was corroborated using the USPTO database. More than 400 key publications for references were consulted. Plants used worldwide to treat anxiety and pharmacologically documented, as well as those used in clinical trials and cited in peer-reviewed international manuscripts, were included. Plants excluded were those empirically used in medicinal practices of anxiety, but without documented pharmacological or scientific studies. All sources utilized were written in English.

The publications that were included in the clinical studies were only those that were validated using the proper scale that measures the severity of anxiety, ie, the Hamilton anxiety (HAMA) scale, considered to be the gold-standard diagnostic tool.

Plants with pharmacological anxiolytic effects

From ancient times, medicinal plants were employed empirically, probably universally, for the treatment of anxiety and related disorders, but pharmacological and toxicological studies rarely existed. Even today, a relatively small number of these plants have been subjected to accepted scientific evaluation for their potential anxiolytic effects. Pharmacological studies with animal models are now used to test traditionally employed plants for their effectiveness in the treatment of anxiety-like behavior. Mice and rats present practical models for testing, due to their reproducibility, control of the inbreeding selection, and rapid response, as well as the possibility to analyze either brain structures or proteins and metabolites linked to the anxiety's phenotype.[10,11] In the past, these animal models subjected to anxiety-producing substances were mainly assessed for their behavior using the hole-board and the light–dark transition tests, because these tests presented a pharmacological specificity where nonanxiolytic psychoactive drugs did not produce false positives.[12] Nowadays, the elevated plus-maze (EPM) test is the model used to define the anxiolytic action of a plant extract in almost 80% of all scientific publications, followed by the light–dark transition (~17%), shock-probe burying (~4%), and hole-board (~2%) models. The EPM test was introduced by Pellow et al in 2005 employing rats,[13] and by Lister in 1987 using mice.[14] This model consists of two open and two enclosed arms, and is based on the natural aversion of rodents to open spaces, thereby avoiding exposure to threatening situations. The EPM test records the number of entries in both arms, where a higher percentage of time spent on the open arms indicates an anxiolytic effect.[15]

A total of 112 species belonging to 63 botanical families that had been subjected to in vivo animal models have been recorded in Table 1. The anxiolytic effects of these plants were determined using the EPM model conducted in mice in most of the species. As shown in Table 1, the Asteraceae, Fabaceae, and Lamiaceae families are the ones with a higher number of documented species. All the listed

Table 1 Plants with pharmacological anxiolytic effect

Family/species	Countries/regions with ethnobotanical use	References
Acoraceae		
Acorus calamus	India/China	16
Aizoaceae		
Sceletium tortuosum	South Africa	17
Amaranthaceae		
Achyranthes aspera	India	18
Annonaceae		
Rollinia mucosa	Mexico	19
Apiaceae		
Bupleurum falcatum	China	20
Centella asiatica	India/China	21
Coriandrum sativum	India/Iran	22
Apocynaceae		
Apocynum venetum	China	23
Rauvolfia ligutrina	Brazil	24
Tabernaemontana divaricata	India	25
Tylophora indica	India	26
Araceae		
Colocasia esculenta	India	27
Araliaceae		
Panax ginseng	China	28
Panax quinquefolium	China	29
Asteraceae		
Artemisia copa	Argentina	30
Lactuca sativa	Egypt	31
Matricaria recutita	Mexico	32
Saussure alappan	India	33
Sonchuso leraceus	Worldwide	34
Sphaeranthus indicus	India	35
Synedrella nodiflora	Ghana	36
Boraginaceae		
Echium amoenum	Iran	37
Calophyllaceae		
Kielmeyera coriacea	Brazil	38
Clusiaceae		
Garcinia kola	Africa	39
Commelinaceae		
Commelina benghalensis	China/Pakistan/India	40
Palisota hirsuta	West Africa	41
Convolvulaceae		
Convolvulus pluricaulis	India	42
Evolvulus alsinoides	India	42
Elaeocarpaceae		
Elaeocarpus sphaericus	India	43
Equisetaceae		
Equisetum arvense	Mexico/Italy	44
Euphorbiaceae		
Emblica officinalis	India	45
Euphorbia hirta	Philippines	46
Fabaceae		
Albizia julibrissin	China	47
Albizia lebbeck	India	48
Astragalus mongholicus	China/Mongolia	49
Bauhinia racemosa	India	50
Caesalpinia bonducella	India/Africa	51
Clitoria ternatea	India	42
Erythrina mulungu	Brazil	52
Erythrina velutina	Brazil	53
Glycyrrhiza glabra	India/China	54
Griffonia simplicifolia	Not reported	55
Sesbania grandiflora	India	56
Gelsemiaceae		
Gelsemium sempervirens	Mexico/US	57
Gentianaceae		
Canscora decussata	India	58
Gentiana kochiana	Central/Northern Europe	59
Ginkgoaceae		
Ginkgo biloba	China	60
Hypericaceae		
Hypericum perforatum	Europe/North America	61
Iridaceae		
Crocus sativus	Iran/China/India	62
Lamiaceae		
Lavandula angustifolia	England/Europe	63
Melissa officinalis	Europe	64
Ocimum sanctum	India	65
Salvia elegans	Mexico	66
Salvia reuterana	Iran	67
Scutellaria baicalensis	China	68
Scutellaria lateriflora	North America	69
Stachys lavanduifolia	Iran	70
Vitex negundo	India	71
Lauraceae		
Cinnamomum cassia	China	72
Lythraceae		
Punica granatum	Worldwide	73
Magnoliaceae		
Schisandra chinensis	China	74
Malpigeaceae		
Galphimia glauca	Mexico	75
		76
Malvaceae		
Theobroma cacao	Not reported	77
Tilia tomentosa	Latin America	78
Meliaceae		
Azadirachta indica	India	79
Moraceae		
Morus alba	China/India	80
Myricaceae		
Myrica nagi	India	81
Nelumbonaceae		
Nelumbo nucifera	India	82
Nymphaeaceae		
Nymphaea alba	Not reported	83
Orchidaceae		
Gastrodia elata	China	84
Oxalidaceae		
Oxalis corniculata	India	85
Papaveraceae		
Eschsholzia californica	US	86
Papilionaceae		
Trigonella foenumgraecum	India	87

(*Continued*)

(*Continued*)

Table 1 (*Continued*)

Family/species	Countries/regions with ethnobotanical use	References
Passifloraceae		
Passiflora alata	Brazil	88
Passiflora edulis	Brazil	88
Passiflora incarnata	North America	89
Phytolaccaceae		
Hilleria latifolia	Ghana	90
Petiveria alliacea	Brazil	91
Pinaceae		
Abies pindrow	India	92
Cedrus deodara	India	93
Piperaceae		
Piper methysticum	North America	94
Poaceae		
Cymbopogon citratus	Brazil/India	95
Polygalaceae		
Securidaca longepedunculata	Africa	96
Portulacaceae		
Portulaca oleracea	China	97
Rhamnaceae		
Ziziphus jujuba	China	98
Rosaceae		
Crataegus oxycantha	India	99
Rubiaceae		
Gardenia jasminoides	Japan	100
Morinda citrifolia	Worldwide	101
Nauclea latifolia	Central Africa	102
Uncaria rhynchophylla	China	103
Rutaceae		
Aeglemar melos	India	104
Citrus aurantium	Brazil/Iran	105
Glycosmis cochinchinensis	China	106
Ruta chalepensis	Mexico	107
Rosaceae		
Rubus brasiliensis	Brazil	108
Salisaceae		
Salix aegyptiaca	Southeast Asia	109
Sapindaceae		
Cardiospermum halicacabum	India	110
Paulina cupana	Brazil	111
Sapindus mukorossi	India	112
Scorphulariaceae		
Bacopa monniera	India	113
Simaroubaceae		
Eurycoma longifolia	Indonesia/Malaysia	114
Solanaceae		
Withania somnifera	India	115
Theaceae		
Camellia sinensis	China/India	116
Tiliaceae		
Tilia americana	Mexico	117
Turneraceae		
Turnera aphrodisiaca	India	118
Urticaceae		
Cecropia glazioui	Latin America	119
Valerianaceae		
Nordostchys jatamansi	India	120
Valeriana officinalis	North America	121
Valeriana wallichii	India	122
Verbenaceae		
Aloysia polystachya	Argentina	123
Vitaceae		
Leea indica	Bangladesh	124
Zinziberaceae		
Zingiber officinalis	South Asia	125

(*Continued*)

species have ethnomedical records in different countries, India (33.4%) and China (16%) being those with the most numerous citations.

Human clinical studies with anxiolytic herbs

Several herbal medicines with anxiolytic effects have been subjected to clinical trials. In Table 2A, plant species with documented use to treat general anxiety disorders are presented, while those used to treat anxiety-associated conditions are recorded in Table 2B. Table 2 shows clinical trials that used a validated scale measuring the severity of anxiety, ie, the HAMA scale, considered the gold-standard diagnostic tool.[126] In addition, scales that measure how the patient is perceived symptomatologically by a physician are also included, as the Physician's Clinical Global Impression scale as well as the Clinical Global Impression-Improvement scale. These scales can measure the improvement of patients shown by reduction in the severity of symptoms. The randomness of the clinical trials is important for its reliability. The trials that were conducted using a contemporarily prescribed and accepted as effective antianxiety drug, indicated the level of effectiveness as related to the known anxiolytic drug, as well as permit a time evaluation as to the anxiolytic effects or the appearance of any adverse effects. With respect to the time of treatment and size of the sample, when compared with clinical trials with synthetic drugs – ie, such selective inhibitors of serotonin recapture as escitalopram and paroxetine, which represent first-line anxiolytic medicine as recommended by the World Federation of Societies of Biological Psychiatry,[127] – the optimum time is 8 or more weeks, if we take into consideration that general anxiety disorder ideally requires a minimum treatment of two months and frequently more. Escitalopram has been studied for 10 weeks using a sample of 177 patients,[128] and for 12 weeks with a sample of 150 patients.[129] Paroxetine was studied for 8 weeks using 237 patients.[130] It is

Table 2 Human clinical trials to treat (**A**) general anxiety disorder and (**B**) anxiety-associated disorders

Plant and clinical trial	Extract (alone or combination)	Dosage and period of time	Sample (number of patients)	Scale	Tolerability, security or LD_{50}	References
(**A**)						
Acorus calamus Clinical open trial	70% hydroethanolic extract	500 mg/capsule, twice daily 60 days	33	BPRS	Well tolerated	16
Centella asiatica Open trial	70% hydroethanolic extract	500 mg/capsule, twice daily 60 days	33	BPRS	ND	21
Eschscholtzia californica Double-blind, randomized, placebo-controlled study	Sympathyl (*Crataegus oxyacantha, Eschscholtzia californica*, and magnesium)	2 tablets twice daily	264	HAMA, PCGI and, PSA	Well tolerated	137
Galphimia glauca Randomized, double-blind, placebo-controlled trial	Hydroethanolic extract	310 mg/capsule twice daily 4 weeks	152	HAMA, CFI-C, CGI-I	Well tolerated and safe	135
Ginkgo biloba Randomized, double-blind, placebo-controlled trial	*Ginkgo biloba* EGb 761 extract	240 and 480 mg daily 4 weeks	107	HAMA, CGI-C, EAAS, PCGI, and B-L	Well tolerated and safe	136
Lavandula Multicenter, double-blind, randomized, lorazepam controlled study	Silexan, oral lavender oil capsule	89 mg/capsule once daily 6 weeks	77	HAMA, SAS, and CGI-I	Well tolerated	138
Lavandula Randomized, double-blind, placebo-controlled trial	Silexan, oral lavender oil capsule	80 mg/capsule once daily 10 weeks	221	HAMA, PSQI, CGI-I, ZSAS	Well tolerated	133
Matricaria recutita Randomized, double-blind, placebo-controlled trial	Extract	220 to 1100 mg daily 8 weeks	57	HAMA, CGI-C, and BAI	Well tolerated	32
Passiflora incarnata Pilot double-blind randomized controlled trial with oxazepam	Extract	45 drops daily 4 weeks	36	HAMA	Well tolerated	139
Piper methysticum Controlled, double-blind, multicenter clinical trial	Kava LI 150 extract	400 mg daily 8 weeks	129	HAMA, BOEAS, CGI-I, Bf-S, SF-B, and AL	Well tolerated	134
Placebo-controlled, double-blind crossover trial	Kava tablets containing 250 mg of kavalactones	250 mg/tablet 5 tablets daily 3 weeks	60	HAMA	Well tolerated and safe	140
Rhodiola rosea A pilot study	Extract	340 mg daily 10 weeks	10	HAMA and CGI-I	Well tolerated	141
Valeriana officinalis Randomized placebo-controlled pilot study	Valepotriate extract	81.3 mg daily 4 weeks	36	HAMA and STAI	ND	142

Table 2 (*Continued*)

Plant and clinical trial	Disorder	Extract or combination	Dosage and period	Sample (number of subjects)	Scale and other studies	Tolerability, security or LD_{50}	References
(B)							
Bacopa monniera Randomized, double-blind, placebo-controlled clinical trial	Healthy elderly with anxiety and depression	Standardized dry extract	300 mg daily 12 weeks	54	STAI	Well tolerated	143
Centella asiatica Double-blind, placebo-controlled study	Anxiety syndrome in healthy subjects	Gotu kola extract	12 g single dose	40	ASR	ND	131
Crocus sativus Open clinical trial, observational	Premenstrual syndrome, dysmenorrhea, and irregular menstruation	Saffron odor	Saffron odor 20 minutes	35	STAI	ND	144
Hypericum perforatum Multicenter, randomized, placebo-controlled	Somatization disorder	Hypericum extract LI 160	600 mg daily 6 weeks	151	HAMA-SOM	Well tolerated	145
Lavandula Randomized double-blind study	Volunteers with anxiety post–film clips	Lavender oil capsules	100, 200 μL single dose	97	STAI	ND	132
Lavandula Cluster randomized controlled trial	Dental patients with anxiety	Lavender oil	Odor of lavender	340	STAI-6 and MDAS	ND	146
Melissa officinalis Prospective, open-label study	Stressed volunteers with mild-to-moderate anxiety disorders and sleep disturbances	Cyracos hydroalcoholic leaf extract	600 mg daily 15-days	20	CGI-I, FRSA, HRSD	Well tolerated	147
Melissa officinalis Double-blind, placebo-controlled, randomized, balanced crossover experiment	Healthy volunteers exposed to stressor simulation	Standardized extract	300 mg and 600 mg single dose	18	DISS battery	ND	148
Panax ginseng Open clinical trial	Postmenopausal women with anxiety	Extract	6 g daily 30 days	12	STAI	ND	149
Passiflora incarnata Double-blind, placebo-controlled study	Patients presurgery	Passipy Iran Darouk (passiflora extract)	500 mg as premedication 90 minutes before surgery 2 doses	60	NRS	ND	150
Passiflora incarnatha Multicenter, double-blind, placebo-controlled study	Patients with adjustment disorder and anxious mood	Euphytose (combination of six extracts: *Crataegus, Ballota, Passiflora Valeriana, Cola, and Paullinia*)	2 tablets 3 times per day 4 weeks	182	HAMA	ND	151
Piper methysticum Randomized, placebo-controlled, double-blind study	Anxiety syndrome	Kava extract WS 1490 (Laitan)	100 mg 3 times per day 4 weeks	58	HAMA, CGI-I	Well tolerated	152

Piper methysticum Multicenter, randomized, placebo-controlled, double-blind trial	Anxiety of nonpsychotic origin	Kava extract WS 1490	25 weeks	101	HAMA, CGI-I, SRSI-90 items	Well tolerated	153
Piper methysticum Randomized, placebo-controlled, double-blind study	Nonpsychotic nervous anxiety, tension, and restlessness states	Kava extract WS 1490	300 mg daily 4 weeks	40	HAMA, EAAS, and CGI-I	Well tolerated	154
Piper methysticum Randomized, placebo-controlled, double-blind, multicenter trial	Neurotic anxiety	Kava extract WS 1490	150 mg daily 4 weeks	141	Bf-S, ASI, CGI-I, EAAS	Well tolerated and safe	155
Valeriana officinalis Double-blind, placebo-controlled, randomized, balanced crossover experiment	Healthy volunteers during laboratory-induced stress	Product containing *Melissa officinalis* and Valeriana officinalis extracts	600, 1200, and 1800 mg single doses	24	DISS battery	ND	156
Withania somnifera Double-blind, placebo-controlled study	Anxiety disorders	Ethanol extract	500 mg daily 6 weeks	39	HAMA, GRS	Well tolerated	157

Abbreviations: HAMA, Hamilton Anxiety Scale; HAMA-SOM, subfactor somatic anxiety; STAI, State-Trait Anxiety Inventory; PCGI, Physician's Clinical Global Impression; PSA, patient self-assessment; CGI-C, Clinical Global Impression of Change; EAAS, Erlangen Anxiety Tension and Aggression Scale; B-L, list of complaints; BAI, Beck Anxiety Inventory; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression-Improvement Scale; FRSA, Free Rating Scale for Anxiety; HRSD, Hamilton Rating Scale for Depression; NRS, Numerical Rating Scale; SRSI-90 Items, Self-Report Symptom Inventory-90 Items; BOEAS, Boerner Anxiety Scale; Bf-S, Self-Rating Scale for Well-Being; SF-B, Sleep Questionnaire; AL, Quality-of-Life Questionnaire; ASI, Anxiety Status Inventory; MDAS, Modified Dental Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index; ZSAS, Zung Self-Rating Anxiety Scale; GRS, Global Rating Scale; ASR, Acoustic Startle Response; ND, not determined.

recommended that clinical trials using plants be performed with the same periods of time and using samples of more than 80 patients so as to be in line with the standards used for anxiolytic drugs. However, studies conducted with smaller groups can be useful as a guide for larger samples and for longer periods of medication. Most of the studies conducted with plants give tolerability data (absence or low frequency of adverse effects), allowing evaluation of the benefits of medicinal plants over such synthetic drugs as benzodiazepines and of inhibitors of serotonin recapture, both of which are the most prescribed anxiolytics. It is also important to conduct studies on children, teenagers and elderly patients. Table 2B shows plants that reduce anxiety in conditions that differ from those of general anxiety disorders, and includes clinical trials using a scale to measure the severity of anxiety. Most clinical trials include small numbers, and in some cases, such as *Centella asiatica*[131] or *Lavandula* spp.[132] one dose is administered, which, if reduction of anxiety is reported, becomes preliminary data of the anxiolytic potential of the plants.

According to the aforementioned criteria, it is possible to consider rigorous studies such as the one with silexan oral lavender oil capsule conducted for 10 weeks in 221 patients,[133] and the one with *Piper methysticum* conducted for 8 weeks with 129 patients,[134] both having tolerability data. Two more studies reaching the required standards are those with *Galphimia glauca* conducted in 152 patients[135] and with *Ginkgo biloba* [136] in 107 patients, both including tolerability and security data.

Active compounds

A total of 33 purified natural compounds (Table 3) with proven anxiolytic activity were recorded from the 112 plants listed in Table 1. The reported compounds include a variety of secondary metabolites, ie, flavonoids, terpenoids, alkaloids, and phenols, with the terpenoids (total 14 compounds) forming the majority of the reported purified natural anxiolytic compounds (>42%), and the flavonoids (nine compounds) forming the second major group. Other secondary metabolites such as alkaloids (five compounds), phenols (four compounds), and other derivatives were less reported.

Mechanism of action

From the literature, it is known that most of the herbal medicines that benefit anxiety disorders had effects on the gamma-aminobutyric acid (GABA) system.[184] The reported mechanisms of action indicate the induction of ionic channel transmission blocking voltage gates or altering

Table 3 Active compounds from anxiolytic plants

Compound	Type of compound	Plant species	References
1-α-hydroxy-erythravine	Alkaloid	*Erythrina mulungu*	158
4-hyroxybenzaldehyde	Phenol	*Gastrodia elata*	84
4-hydroxybenzyl alcohol	Phenol	*Gastrodia elata*	84
6-methylapigenin	Flavonoid	*Valeriana officinalis/Valeriana wallichii*	159
			160
Apigenin	Flavonoid	*Matricaria recutita/Turnera aphrodisiaca*	161
			162
Bacoside A	Terpenoid	*Bacopa monniera*	163
Baicalein	Flavonoid	*Scutellaria baicalensis*	164
Baicalin	Flavonoid	*Scutellaria lateriflora*	165
Cardiospermin	Cyanogenic-glucoside	*Cardiospermum halicacabum*	110
Chrysin	Flavonoid	*Passiflora incarnata*	166
Crocins	Terpenoid	*Crocus sativus*	167
Dihydrokavain	Terpenoid	*Piper methysticum*	168
Essential oil	Terpenoid	*Citrus aurantiuman*	169
Essential oil	Terpenoid	*Cymbopo goncitratus*	170
Erysothrine	Alkaloid	*Erythrina mulungu*	171
Erythravine	Alkaloid	*Erythrina mulungu*	158
Galphimines A-I	Terpenoid	*Galphimia glauca*	172
Geniposide	Terpenoid	*Gardeniae jasminoides*	100
Ginkgolic acid conjugates	Phenol	*Ginkgo biloba*	173
Ginsenoside Rb1	Terpenoid	*Panax ginseng*	174
Ginsenosides Rg3 and Rh2	Terpenoid	*Panax ginseng*	175
Ginkgolide-A	Terpenoid	*Ginkgo biloba*	
Kaempferol	Flavonoid	*Apocynum venetum/Tilia americana*	176
			177
Mangiferin	Phenol	*Canscora decussata*	58
Neferine	Alkaloid	*Nelumbo nucifera*	178
Quercetin	Flavonoid	*Tilia americana*	177
Safranal	Terpenoid	*Crocus sativus*	
Sanjoinine A	Alkaloid	*Ziziphus jujube*	179
Seed oil	Terpenoid	*Lactuca sativa*	180
Tiliroside	Flavonoid	*Tilia americana*	181
Valepotriates	Terpenoid	*Valeriana officinalis*	142
Valerenic acid	Terpenoid	*Valeriana officinalis*	182
Wogonin	Flavonoid	*Scutellaria baicalensis*	183

membrane structures.[185] GABA transaminase or glutamic acid decarboxylase inhibition has also been reported.[186]

In some cases, the herbal anxiolytic action was attributed to binding with benzodiazepine receptor sites (eg, α-subunit).[187] The increased GABA neurotransmission that subsequently followed had a damping effect on stimulatory pathways, which ultimately provided a psychologically calming effect.[188] In Table 4, the mechanism of action of 33 extracts or purified compounds from herbal medicines to treat anxiety is detailed. This search was done for the 112 plants presented in Table 1 as well as for the compounds compiled in Table 3. A total of 33 plant extracts or purified compounds were identified in several databases. On the basis of the data in Table 4, it can be concluded that most of the plant extracts and purified anxiolytic compounds function through the GABAergic mechanism (more than 72%, 24 total entries), and the rest (nine entries) utilize a combination of adrenergic, dopaminergic, and serotonergic mechanisms.

Patent applications on plants with anxiolytic action

A patent search was conducted using Espacenet database from the European Patent Office and corroborated by the United States Patent and Trademark Office (USPTO) database. The patent information covered the keywords plant, herbal, and extract, and these were cross-linked with anxiety and anxiolytic terms. Distillation of the final search resulted in a total of 47 patent applications for plants used as anxiolytic purposes. The adopted criteria used documentation written in English in which the anxiolytic activity was clearly demonstrated, and excluded those patents either without scientific backing or written in any language other

Table 4 Mechanism of action of herbal anxiolytics extracts or compounds

Plant species	Extract/compound	Mechanism of action	References
Acorus calamus	Aqueous ethanol extract	Adrenergic and dopaminergic	189
Albizzia lebbeck	*n*-Butanol fraction	GABAergic	48
Albizzia julibrissin	Aqueous extract	Serotonergic	47
Aloysia polystachya	Hydroethanol extract	Mediated by other mechanism than GABAa receptors	190
Apocynum venetum	Ethanol extract	GABAergic	23
Bupleurum falcatum	Alcohol extract	Adrenergic mechanisms	20
Cedrus deodara	Alcohol extract	GABAergic	93
Convolvulus pluricaulis	Chloroform fraction of total ethanol extract	Adrenergic, dopaminergic, and serotonergic systems	191
Cinnamomum cassia	Ethanol extract	Serotonergic and GABAergic	72
Crataegus oxyacantha	Alcohol extract	GABAergic	99
Cymbopogon citratus	Essential oil	GABAergic	170
Erythrina velutina	Alcohol extract	GABAergic	192
Gardeniae jasminoides	Standardized extract	GABAa	193
Gastrodia elata	4-Hyroxybenzaldehyde	GABAergic	84
Gastrodia elata	4-Hydroxybenzyl alcohol	Serotonergic	84
Melissa officinalis	Cyracos standardized alcohol extract	GABAergic	194
Morinda citrifolia	Methanol extract	GABAa	101
Nelumbo nucifera	Aqueous extracts	GABAergic	82
Palisota hirsuta	Ethanol extract	GABAergic	41
Panax ginseng	Ginsenosides Rg3 and Rh2	GABAergic	175
Passiflora incarnata	Commercial extract	GABAergic	195
Paulina cupana	Semipurified extract	Dopaminergic and serotonergic systems	111
Piper methysticum	Ethanol extract	GABAa	94
Rollinia mucosa	Hexane extract	GABA	19
Rubus brasiliensis	Hexane extracts	GABAa	108
Scutellaria ebaicalensis	Baicalein	GABAergic	164
Scutellaria lateriflora	Baicalin	GABAa	165
Scutellaria baicalensis	Wogonin	GABAa	183
Ziziphus jujuba	Alcoholic extract	GABAergic	196
Uncaria rhynchophylla	Aquous extract	Serotonergic	103
Valeriana wallichii	6-Methylapigenin	GABAa	159
Valeriana officinalis	Valerenicacid	GABAa	182
Ziziphus jujuba	Sanjoinine A	GABAergic	179

Abbreviation: GABA, gamma-aminobutyric acid.

than English. The first patent in this review was granted in 1967 by a Belgian company, in which the action of glaziovine, an alkaloid isolated from *Ocotea*, was registered to treat anxiety and depression. It is very difficult to obtain statistics for the global market involving the commercialization of anxiolytic plants and extracts, because most of the producers and exporters of such material come from underdeveloped countries where strict governmental control of data is lacking. The purpose of this review is to offer a record of the most important worldwide anxiolytic medicinal plants with high economic impact, as expressed by patent applications.

A total of 47 registered patent applications for anxiolytic plants were found. Of these, only seven were exclusively for the treatment of anxiety, while the rest reported medicinal use for additional disorders, basically for depression and stress. The four with the most patents are *Valeriana officinalis*, *Piper methysticum* (kava), *Ziziphus jujuba* (jujube), and *Hypericum perforatum*, each of which had five patents. Concerning these patents, 20 presented only one plant, 16 combined a mixture of other plants and isolated compounds, while six were for a plant mixed with purified compounds or extracts (Table 5).

The kava root presents an interesting case. Used in various Pacific Basin countries as a traditional beverage for soporific and narcotic effects, it was introduced into the US market in the 1990s, principally as an antianxiety preparation. The bioactive kavalactones have been used for standardization in phytomedicines, acting very positively to decrease anxiety without the loss of mental acuity, as well as in dietary supplements. Although kava efficacy has been well established, in 2001several fatal cases of hepatotoxicity among Westerners who consumed kava attracted the attention of the scientific community. The Food and Drug Administration (FDA) issued

Table 5 Patent registration for plants with anxiolytic action

Plant species/genus (family)	Part used or process	Alone or in combination	Country	Year	Patent application number	Other medicinal uses
Lavandula angustifolia (Lamiaceae)	NR	*Humulus lupulus* L., *Melissa officinalis* L., *Passiflora incarnata* L., *Valeriana officinalis* L.	Germany	2011	WO2011EP51604	Dyssomnia
Punica granatum (Lythraceae)	Pulp	Alone	Korea	2011	WO2011 KR02453	Depression, attention disorders
Theobroma cacao (Sterculiaceae)	Beans	Alone	US	2010	US20100597550	Dysphoria, depression, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders, bulimia, substance abuse, panic disorder, premenstrual syndrome, and migraine
Ziziphus jujuba (Rhamnaceae)	Seeds	*Digitalis* sp., *Angelica gigas*, *Curcuma longa*	Korea	2009	KR20090131938	Stress
Valeriana officinalis (Valerianaceae)	Roots	*Origanum* sp., *Thymus* sp., *Hypericumperforatum*, *Inulahelenium*	Russia	2009	RU20090132033	Stress, sleep disturbance, antioxidant
Morinda citrifolia (Rubiaceae)	Roots	Alone	China	2009	CN20091162467	Antidepressant
Astragalus (Leguminosae)	Roots	*Arctium lappa*, *Polygonatum* sp., *Rehmannia* sp.	China	2009	CN20091218322	Insufficiency of heart and spleen, deficiency of liver-yin and kidney-yin, headache and dizziness, exhaustion and fatigue, insomnia and forgetfulness, depression, palpitation, night sweats
Galphimia glauca (Malpighiaceae)	Aerial parts	Alone	Mexico	2009	MX20090007792	
Ziziphus jujuba (Rhamnaceae)	NR	Jujuboside, saponins of lily, *Polygonum* sp., pilose antler, Epimedium sp., *Zingiber officinale*, glycyrrhizic acid	China	2009	CN20091067127	Insomnia, short memory, dizziness and tinnitus, palpitation
Camellia sinensis (Theaceae)	Leaves	Theanine, *Panax* sp., or *Sasamorpha* sp.	Korea	2009	KR20090030428	Relieving stress
Valeriana officinalis (Valerianaceae)	Roots	*Crataegus* sp., *Leonurus cardiaca*, *Inula helenium*, *Glyccyrrihiza uralenzis* or *Glycyrrhiza glabra*, *Hypericum perforatum*, *Papaver* sp.	Russia	2008	RU20080150453	Stabilize arterial pressure, contributes to cessation of retrosternal pain, depression, and insomnia
Ziziphus jujuba (Rhamnaceae)	Seeds	*Platycladusorientalis*, *Pueraria* sp., *Smilax glabra*, *Prunus persica*, *Panaxginseng*	China	2008	CN20081236792	Promoting sleep, relieving stress

Sceletium tortuosum (Mesembryanthemaceae)	NR	Mesembrine and related compounds	Japan	2008	JP20080272215	Depressive state, psychological or psychiatric disorders with alcohol and drug dependence, bulimia nervosa, and obsessive–compulsive disorders
Morus alba L. (Moraceae)	Leaves	Alone	Korea	2008	KR20080083509	Preventing coronary artery diseases, hyperlipidemia, degenerative arthritis, melancholia
Ginkgo biloba (Ginkgoaceae)	Leaves	Alone	Japan	2008	WO2008JP60477	Antidepressant activity
Gardenia jaminoides (Rubiaceae)	Fruit	Alone	China	2008	CN20081016679	Preventing and/or curing depressive anxiety
Bupleurum (Apiaceae)	Roots	*Cyperus* sp., *Citrus medica*, *Poncirus trifoliata*, *Gentiana lutea*, *Sinapsis alba*, *Acorus calamus*, *Rehmannia* sp., *Albizia julibrissin*, *Polygonum multiflorum*, *Ziziphus jujuba*, *Polygala* sp., *Coptis* sp., *Glycyrrhiza glabra*	China	2007	CN20071015237	
Erythrina mulungu (Fabaceae)	Hydroalcohol extract	Alone	Brazil	2007	MX20070004690	
Ziziphus jujube (Rhamnaceae)	Seeds	Alone	China	2007	CN20071053859	Dysphoria
Matricaria recutita (Asteraceae)	NR	*Salvia* sp., *Bidens* sp., *Urtica* sp., *Rosa* sp., *Vaccinium* sp., *Eucalyptus* sp., *Tanacetum* sp., *Achillea* sp.*Calendula* sp.	Russia	2006	RU20060145809	Correcting human psychoemotional state for the purpose of removing feelings of aggression, despair, reserve, depression
Bupleurum falcatum (Apiaceae)	Water extract	Alone	Korea	2006	KR20060094166	Inflammatory liver diseases, asthma, arthritis, diabetes, depression, vasodilation, vomiting, pain
Valeriana officinalis (Valerianaceae)	Roots	*Proanthocyanidin*, vitamins E, B_3, B_6, B_{12}, L-theanine, magnesium	US	2006	US20060413648	Sleep disorders, reduction of stress
Cinnamomum (Lauraceae)	Bark	Cinnamaldehyde extract	China	2006	CN20061054874	Dysphoria, depression, neurasthenia
Valeriana wallichii (Valerianaceae)	NR	Alone	China	2005	CN20051021662	Dysphoria
Salix (Salicaceae)	NR	Alone	Germany	2004	WO2004EP14780	Antidepressant, neuroleptic, tranquilizer, sleeping disorders
Eschscholzia californica (Papaveraceae)	NR	*Valeriana officinalis*	France	2004	FR20040012531	Tranquilizer, hypnotic
Cinnamomumcassia (Lauraceae)	Bark	Alone	Korea	2004	KR20040079325	NR

(*Continued*)

Table 5 (*Continued*)

Plant species/genus (family)	Part used or process	Alone or in combination	Country	Year	Patent application number	Other medicinal uses
Piper methysticum (Piperaceae)	NR	Theobromine	US	2004	US20040945108	Fatigue, muscle tension, nervous depression, headache, obesity, and mild pain, as well enhancement of cognition and mental focus
Piper methysticum (Piperaceae)	NR	With one or more anxiolytics	US	2004	US20040945106	NR
Piper methysticum (Piperaceae)	*Piper methystine*–free extract	Alone	Germany	2004	DE200410039012	Tranquilizer
Scutellarialateriflora (Lamiaceae)	Standardized extracts	Alone	US	2004	US20040852660	Insomnia, convulsions, muscle tension, spasm
Cnidium officinale (Apiaceae)	Rhizomes	Alone	Korea	2004	KR20040114525	Antispasmodic and preventing hypertension
Nelumbo nucifera (Nelumbonaceae)	Seeds	*Rehmannia glutinosa*, *Pachyma hoelen*, *Perilla frutescens*	Japan	2004	JP20040039362	NR
Anemarrhena asphodeloides (Liliaceae)	Rhizome		Korea	2004	KR20040114532	Antipyretic and hypoglycemic action
Leonurus cardiaca (Lamiaceae)	Alcohol extract	*Melissa officinalis*, *Rosa* sp., *Echinacea purpurea*, *Crataegus* sp.	Russia	2003	RU20030136406	Sedative
Panax (Araliacea)	NR	Alone	Korea	2003	KR20030070249	NR
Glycyrrhiza uralensis (Fabaceae)	Roots	Liquiritigenin	Korea	2003	KR20030068777	Diseases caused by heavy-metal poisoning, ie, anemia, hemoglobinuria, hematuria, jaundice, nausea, vomiting, abdominal pain, breathing disorder, respiratory distress, anxiety, fatigue, nerve injury, or memory impairment
Griffonia simplicifolia (Fabaceae)	Seeds	Extract of plants rich in 5-hydroxytriptophane	Spain	2002	ES20020002936	Syndromes related to fatigue, including pain, muscular problems, depression
Scutellaria lateriflora (Lamiaceae)	NR	Alone	US	2002	WO2002US29309	Insomnia, convulsions, muscle tension, spasm
Hypericum perforatum (Hypericaceae)	NR	Magnesium asparaginate, *Rhodiola rosea*, *Coffea arabica*, flower pollen, *Theobroma cacao*	Russia	2002	RU20020120352	Nervopsychic stress, fear
Hypericum perforatum (Hypericaceae)	NR	Acetyl-L-carnitine in combination with hypericin	Italy	2000	US20000719551	Nervous alteration due to an anxious state, irritability, or depression
Ginkgo biloba (Ginkgoaceae)	Leaves	Alone	Bulgaria	2000	BG20000104970U	Memory, senile dementia, vertigo, headache, depression, migraine, neuralgia, sexual potency, strengthening of the immune system, atherosclerosis

Hypericum perforatum (Hypericaceae)		Vitamin A, C and E, iron, manganese, zinc	Bulgaria	1998	BG19980102723U	Depression, suppression, fear neurosis and insomnia, digestive disorders, stomach and duodenal ulcers, enterocolitis, atherosclerosis, immune defence
Piper methysticum (Piperaceae)	Roots	*Passiflora* sp., *Matricaria chamomilla*, *Humulus lupulus*, *Schisandra* sp.	US	1998	US19980102165	Stress
Crataegus oxyacantha (Rosaceae)	NR	Magnesium salt, *Eschscholzia californica*	France	1996	FR19960000553	NR
Piper methysticum (Piperaceae)	Roots	Cross-linked cellulose carrier	Germany	1995	EP19950100411	Tension and restlessness
Ginkgo biloba (Ginkgoaceae)	Leaves	Increased bilobalide content	Germany	1994	US19940244900	Antidepressant

Abbreviation: NR, not reported.

a customer advisory regarding the dangers of this agent in 2002. Its use is banned in several European countries. Nevertheless, a lot of doubts surround this issue because many data do not support a hepatotoxic potential, and the affected patients reported in the literature were also on other medications.

Although India possesses both an extraordinary flora and ancient knowledge based on the Ayurvedic legacy, it has no patent record in line with the criteria established. Three Indian patent applications, for *Musa* spp, *Cassia tora*, and *Myristica fragrans*, were excluded from our table because of a lack of scientific studies employing animals or clinical trials, despite a large body of ethnopharmacological evidence. However, a report in India indicated that 22 plants were patented for the treatment of brain and neurological disorders, occupying eighth position in the list of locally patented species, while the first position was for disorders of the digestive system, with a total of 81 species registered to 2005.[197]

Korea is the country with the most patent applications for anxiolytic plants, followed by China (Figure 1). Both countries have a long history of growing, using, and exporting traditional plant medicines. The number of stores and people involved in the trade of medicinal herbs has been growing through the centuries. After the opening of ports to Western trade, those in the traditional herbal medicines field faced the influx of Western medicines and secured their position in the plant trade by adapting a system of patenting the herbal remedies that they produced and sold.[198]

Both Brazil and Mexico have a megadiversity of flora and widespread traditional use of medicinal plants, and yet have only one patent application each. The analysis of the history of medicinal practices and uses in these two countries, with the lack of respect for indigenous knowledge, medicinal systems, and lack of official interests to establish priorities for the bioprospection of natural resources, combined with

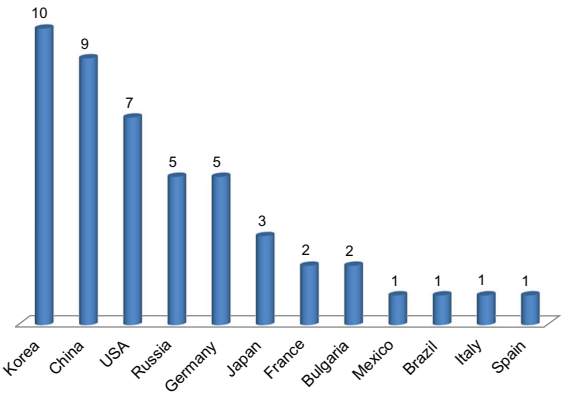

Figure 1 Number of species reported for anxiolytic uses in patents applied for by different countries.

the imposition of allopathic medicines, go a long way towards explaining this situation.

Ethical discussions about biopiracy and the need to respect and protect indigenous and local community knowledge and biological resources, have emerged recently. Herbal drugs are gaining attention, mainly in developing countries due to their huge potential for new medicines, and focus is growing on patents because they contain formulations with multiherb composition, which have the potential to produce desired synergistic action with fewer deleterious side effects.

In spite of the high incidence and broad impact that anxiety has on the quality of human life, today there are no available laboratory tests to diagnose this worldwide health problem. Anxiety is usually diagnosed by means of psychological assessment criteria, interpreted by observation of the patient's behavior, taking into consideration his condition, historical background, and familial occurrences. Mental health professionals can make use of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, known as the DSM-IV, a manual published by the American Psychiatric Association with the aim of reaching a better understanding of the patient's illness and potential treatment.

Genetic factors associated with anxiety are complex and diverse. Advances in molecular biology techniques have allowed for the manipulation of gene expression within the central nervous system of mice in order to better understand the anxiety process at a molecular level.[10] In future, individualized diagnosis and treatment for anxiety patients will be possible to prescribe based on patients' genetic profiling and on the levels of specific biomarkers through proteome and metabolome approaches. Therefore, it will be possible to know the real status of the biochemical routes involved in the pathology of anxiety, much beyond that provided by the monoamine systems. A breakthrough investigation was conducted by Filiou et al in 2011,[11] in which they used endophenotype mice with a defined genetic background for high, normal, and low anxiety-related behaviors, and then compared them in terms of protein expression and presence of metabolites. The resulting proteomic and metabolomic information was combined and processed, and in silico analysis allowed for the identification of crucial metabolic networks responsible for anxiety response. They found altered levels of up to 300 proteins and metabolites between mice with high- and low-anxiety behavior, and highlighted the role of the mitochondria in modulating this action. Knowledge of mitochondrial influence in anxiety disorders is very limited. The authors proposed the mitochondria as the unifying link between energy metabolism, oxidative stress, and neurotransmission alterations observed for the anxiety behavior, indicating the mitochondria as a selective target in the development of new drugs to treat anxiety disorders.

Conclusion

Even though research is increasing in the area of psychopharmacology, until now no comprehensive review exists that explores the use of plants to treat anxiety disorders from various experimental approaches. Using a focused multidisciplinary context, as is presented here, which includes integrated information of in vivo pharmacological studies, as well as clinical trials and molecular targets, it becomes possible to obtain insights into this field and point out future directions. Although there exist several actual reported clinical trials that provide preliminary, positive evidence of anxiolytic effects, few rigorous studies of 8 weeks or more comparing the effect produced by plants with those obtained from the use of synthetic drugs are currently available. This situation clearly indicates that it is time to increase the number of experimental studies, and to conduct rigorous clinical trials with anxiolytic plants and their active compounds.

Moreover, there is still a need for scientifically based information concerning the safety, efficacy, and quality control in the use of anxiolytic plants. One example illustrating the need for quality control and analysis of toxicity is provided by the currently popular use of St John's wort. HIV patients are now told not to use this herbal remedy because it has been shown to create resistance to the currently approved HIV treatment.

This is the first review to offer a compilation of registered patents for anxiolytic plant preparations around the world. One observation on patents is that it would clearly be beneficial to include rigorous clinical trials. The use of the emerging "omics" technology can open a whole new efficient way of understanding the mechanism of action by which many plant extracts and their active compounds exert their pharmacological properties, and stimulate future research with anxiolytic herbal medicines.

Disclosure

The authors report no conflicts of interest in this work.

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