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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		
<i>Acorus calamus</i>	India/China	16
Aizoaceae		
<i>Sceletium tortuosum</i>	South Africa	17
Amaranthaceae		
<i>Achyranthes aspera</i>	India	18
Annonaceae		
<i>Rollinia mucosa</i>	Mexico	19
Apiaceae		
<i>Bupleurum falcatum</i>	China	20
<i>Centella asiatica</i>	India/China	21
<i>Coriandrum sativum</i>	India/Iran	22
Apocynaceae		
<i>Apocynum venetum</i>	China	23
<i>Rauvolfia ligustrina</i>	Brazil	24
<i>Tabernaemontana divaricata</i>	India	25
<i>Tylophora indica</i>	India	26
Araceae		
<i>Colocasia esculenta</i>	India	27
Araliaceae		
<i>Panax ginseng</i>	China	28
<i>Panax quinquefolium</i>	China	29
Asteraceae		
<i>Artemisia copa</i>	Argentina	30
<i>Lactuca sativa</i>	Egypt	31
<i>Matricaria recutita</i>	Mexico	32
<i>Saussure alappan</i>	India	33
<i>Sonchus oleraceus</i>	Worldwide	34
<i>Sphaeranthus indicus</i>	India	35
<i>Synedrella nodiflora</i>	Ghana	36
Boraginaceae		
<i>Echium amoenum</i>	Iran	37
Calophyllaceae		
<i>Kielmeyera coriacea</i>	Brazil	38
Clusiaceae		
<i>Garcinia kola</i>	Africa	39
Commelinaceae		
<i>Commelina benghalensis</i>	China/Pakistan/India	40
<i>Palisota hirsuta</i>	West Africa	41
Convolvulaceae		
<i>Convolvulus pluricaulis</i>	India	42
<i>Evolvulus alsinoides</i>	India	42
Elaeocarpaceae		
<i>Elaeocarpus sphaericus</i>	India	43
Equisetaceae		
<i>Equisetum arvense</i>	Mexico/Italy	44
Euphorbiaceae		
<i>Emblica officinalis</i>	India	45
<i>Euphorbia hirta</i>	Philippines	46
Fabaceae		
<i>Albizia julibrissin</i>	China	47
<i>Albizia lebbeck</i>	India	48
<i>Astragalus mongholicus</i>	China/Mongolia	49
<i>Bauhinia racemosa</i>	India	50
<i>Caesalpinia bonducella</i>	India/Africa	51
<i>Clitoria ternatea</i>	India	42

(Continued)

Table 1 (Continued)

Family/species	Countries/regions with ethnobotanical use	References
<i>Erythrina mulungu</i>	Brazil	52
<i>Erythrina velutina</i>	Brazil	53
<i>Glycyrrhiza glabra</i>	India/China	54
<i>Griffonia simplicifolia</i>	Not reported	55
<i>Sesbania grandiflora</i>	India	56
Gelsemiaceae		
<i>Gelsemium sempervirens</i>	Mexico/US	57
Gentianaceae		
<i>Canscora decussata</i>	India	58
<i>Gentiana kochiana</i>	Central/Northern Europe	59
Ginkgoaceae		
<i>Ginkgo biloba</i>	China	60
Hypericaceae		
<i>Hypericum perforatum</i>	Europe/North America	61
Iridaceae		
<i>Crocus sativus</i>	Iran/China/India	62
Lamiaceae		
<i>Lavandula angustifolia</i>	England/Europe	63
<i>Melissa officinalis</i>	Europe	64
<i>Ocimum sanctum</i>	India	65
<i>Salvia elegans</i>	Mexico	66
<i>Salvia reuterana</i>	Iran	67
<i>Scutellaria baicalensis</i>	China	68
<i>Scutellaria lateriflora</i>	North America	69
<i>Stachys lavandulifolia</i>	Iran	70
<i>Vitex negundo</i>	India	71
Lauraceae		
<i>Cinnamomum cassia</i>	China	72
Lythraceae		
<i>Punica granatum</i>	Worldwide	73
Magnoliaceae		
<i>Schisandra chinensis</i>	China	74
Malpigeaceae		
<i>Galphimia glauca</i>	Mexico	75
		76
Malvaceae		
<i>Theobroma cacao</i>	Not reported	77
<i>Tilia tomentosa</i>	Latin America	78
Meliaceae		
<i>Azadirachta indica</i>	India	79
Moraceae		
<i>Morus alba</i>	China/India	80
Myricaceae		
<i>Myrica nagi</i>	India	81
Nelumbonaceae		
<i>Nelumbo nucifera</i>	India	82
Nymphaeaceae		
<i>Nymphaea alba</i>	Not reported	83
Orchidaceae		
<i>Gastrodia elata</i>	China	84
Oxalidaceae		
<i>Oxalis corniculata</i>	India	85
Papaveraceae		
<i>Eschscholzia californica</i>	US	86
Papilionaceae		
<i>Trigonella foenumgraecum</i>	India	87

(Continued)

Table 1 (Continued)

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

(Continued)

Table 1 (Continued)

Family/species	Countries/regions with ethnobotanical use	References
<i>Valeriana officinalis</i>	North America	121
<i>Valeriana wallichii</i>	India	122
Verbenaceae		
<i>Aloysia polystachya</i>	Argentina	123
Vitaceae		
<i>Leea indica</i>	Bangladesh	124
Zinziberaceae		
<i>Zingiber officinalis</i>	South Asia	125

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

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)							
<i>Bacopa monniera</i> 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
<i>Centella asiatica</i> Double-blind, placebo-controlled study	Anxiety syndrome in healthy subjects	Gotu kola extract	12 g single dose	40	ASR	ND	131
<i>Crocus sativus</i> Open clinical trial, observational	Premenstrual syndrome, dysmenorrhea, and irregular menstruation	Saffron odor	Saffron odor 20 minutes	35	STAI	ND	144
<i>Hypericum perforatum</i> Multicenter, randomized, placebo-controlled	Somatization disorder	Hypericum extract LI 160	600 mg daily 6 weeks	151	HAMA-SOM	Well tolerated	145
<i>Lavandula</i> Randomized double-blind study	Volunteers with anxiety post-film clips	Lavender oil capsules	100, 200 µL single dose	97	STAI	ND	132
<i>Lavandula</i> Cluster randomized controlled trial	Dental patients with anxiety	Lavender oil	Odor of lavender	340	STAI-6 and MDAS	ND	146
<i>Melissa officinalis</i> Prospective, open-label study	Stressed volunteers with mild-to-moderate anxiety disorders and sleep disturbances	Cyrcos hydroalcoholic leaf extract	600 mg daily 15-days	20	CGI-I, FRSA, HRSD	Well tolerated	147
<i>Melissa officinalis</i> 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
<i>Panax ginseng</i> Open clinical trial	Postmenopausal women with anxiety	Extract	6 g daily 30 days	12	STAI	ND	149
<i>Passiflora incarnata</i> Double-blind, placebo-controlled study	Patients presurgery	Passify Iran Darouk (passiflora extract)	500 mg as premedication 90 minutes before surgery 2 doses	60	NRS	ND	150
<i>Passiflora incarnata</i> Multicenter, double-blind, placebo-controlled study	Patients with adjustment disorder and anxious mood	Euphytose (combination of six extracts: <i>Crataegus</i> , <i>Ballota</i> , <i>Passiflora Valeriana</i> , <i>Cola</i> , and <i>Paulinia</i>)	2 tablets 3 times per day 4 weeks	182	HAMA	ND	151
<i>Piper methysticum</i> 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

<i>Piper methysticum</i> 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
<i>Piper methysticum</i> 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
<i>Piper methysticum</i> 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
<i>Valeriana officinalis</i> Double-blind, placebo-controlled, randomized, balanced crossover experiment	Healthy volunteers during laboratory-induced stress	Product containing <i>Melissa officinalis</i> and <i>Valeriana officinalis</i> extracts	600, 1200, and 1800 mg single doses	24	DISS battery	ND	156
<i>Withania somnifera</i> 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, subsfactor somatic anxiety; STAI, State-Trait Anxiety Inventory; PCGI, Physician's Clinical Global Impression; 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 patients¹³⁵ 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	<i>Erythrina mulungu</i>	158
4-hydroxybenzaldehyde	Phenol	<i>Gastrodia elata</i>	84
4-hydroxybenzyl alcohol	Phenol	<i>Gastrodia elata</i>	84
6-methylapigenin	Flavonoid	<i>Valeriana officinalis/Valeriana wallichii</i>	159
			160
Apigenin	Flavonoid	<i>Matricaria recutita/Turnera aphrodisiaca</i>	161
			162
Bacoside A	Terpenoid	<i>Bacopa monniera</i>	163
Baicalein	Flavonoid	<i>Scutellaria baicalensis</i>	164
Baicalin	Flavonoid	<i>Scutellaria lateriflora</i>	165
Cardiospermin	Cyanogenic-glucoside	<i>Cardiospermum halicacabum</i>	110
Chrysin	Flavonoid	<i>Passiflora incarnata</i>	166
Crocins	Terpenoid	<i>Crocus sativus</i>	167
Dihydrokavain	Terpenoid	<i>Piper methysticum</i>	168
Essential oil	Terpenoid	<i>Citrus aurantium</i>	169
Essential oil	Terpenoid	<i>Cymbopo gonicitratus</i>	170
Erysothrine	Alkaloid	<i>Erythrina mulungu</i>	171
Erythravine	Alkaloid	<i>Erythrina mulungu</i>	158
Galphimines A-I	Terpenoid	<i>Galphimia glauca</i>	172
Geniposide	Terpenoid	<i>Gardeniae jasminoides</i>	100
Ginkgolic acid conjugates	Phenol	<i>Ginkgo biloba</i>	173
Ginsenoside Rb1	Terpenoid	<i>Panax ginseng</i>	174
Ginsenosides Rg3 and Rh2	Terpenoid	<i>Panax ginseng</i>	175
Ginkgolide-A	Terpenoid	<i>Ginkgo biloba</i>	
Kaempferol	Flavonoid	<i>Apocynum venetum/Tilia americana</i>	176
			177
Mangiferin	Phenol	<i>Canscora decussata</i>	58
Neferine	Alkaloid	<i>Nelumbo nucifera</i>	178
Quercetin	Flavonoid	<i>Tilia americana</i>	177
Safranal	Terpenoid	<i>Crocus sativus</i>	
Sanjoinine A	Alkaloid	<i>Ziziphus jujube</i>	179
Seed oil	Terpenoid	<i>Lactuca sativa</i>	180
Tiliroside	Flavonoid	<i>Tilia americana</i>	181
Valepotriates	Terpenoid	<i>Valeriana officinalis</i>	142
Valerenic acid	Terpenoid	<i>Valeriana officinalis</i>	182
Wogonin	Flavonoid	<i>Scutellaria baicalensis</i>	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
<i>Acorus calamus</i>	Aqueous ethanol extract	Adrenergic and dopaminergic	189
<i>Albizzia lebbek</i>	<i>n</i> -Butanol fraction	GABAergic	48
<i>Albizzia julibrissin</i>	Aqueous extract	Serotonergic	47
<i>Aloysia polystachya</i>	Hydroethanol extract	Mediated by other mechanism than GABAa receptors	190
<i>Apocynum venetum</i>	Ethanol extract	GABAergic	23
<i>Bupleurum falcatum</i>	Alcohol extract	Adrenergic mechanisms	20
<i>Cedrus deodara</i>	Alcohol extract	GABAergic	93
<i>Convolvulus pluricaulis</i>	Chloroform fraction of total ethanol extract	Adrenergic, dopaminergic, and serotonergic systems	191
<i>Cinnamomum cassia</i>	Ethanol extract	Serotonergic and GABAergic	72
<i>Crataegus oxyacantha</i>	Alcohol extract	GABAergic	99
<i>Cymbopogon citratus</i>	Essential oil	GABAergic	170
<i>Erythrina velutina</i>	Alcohol extract	GABAergic	192
<i>Gardenia jasminoides</i>	Standardized extract	GABAa	193
<i>Gastrodia elata</i>	4-Hydroxybenzaldehyde	GABAergic	84
<i>Gastrodia elata</i>	4-Hydroxybenzyl alcohol	Serotonergic	84
<i>Melissa officinalis</i>	Cyracos standardized alcohol extract	GABAergic	194
<i>Morinda citrifolia</i>	Methanol extract	GABAa	101
<i>Nelumbo nucifera</i>	Aqueous extracts	GABAergic	82
<i>Palisota hirsuta</i>	Ethanol extract	GABAergic	41
<i>Panax ginseng</i>	Ginsenosides Rg3 and Rh2	GABAergic	175
<i>Passiflora incarnata</i>	Commercial extract	GABAergic	195
<i>Paulina cupana</i>	Semipurified extract	Dopaminergic and serotonergic systems	111
<i>Piper methysticum</i>	Ethanol extract	GABAa	94
<i>Rollinia mucosa</i>	Hexane extract	GABA	19
<i>Rubus brasiliensis</i>	Hexane extracts	GABAa	108
<i>Scutellaria ebaicalensis</i>	Baicalin	GABAergic	164
<i>Scutellaria lateriflora</i>	Baicalin	GABAa	165
<i>Scutellaria baicalensis</i>	Wogonin	GABAa	183
<i>Ziziphus jujuba</i>	Alcoholic extract	GABAergic	196
<i>Uncaria rhynchophylla</i>	Aquous extract	Serotonergic	103
<i>Valeriana wallichii</i>	6-Methylpigenin	GABAa	159
<i>Valeriana officinalis</i>	Valerenic acid	GABAa	182
<i>Ziziphus jujuba</i>	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 2001 several 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
<i>Lavandula angustifolia</i> (Lamiaceae)	NR	<i>Humulus lupulus</i> L., <i>Melissa officinalis</i> L., <i>Passiflora incarnata</i> L., <i>Valeriana officinalis</i> L.	Germany	2011	WO2011EP51604	Dyssomnia
<i>Punica granatum</i> (Lythraceae)	Pulp	Alone	Korea	2011	WO2011KR02453	Depression, attention disorders
<i>Theobroma cacao</i> (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 Stress
<i>Ziziphus jujuba</i> (Rhamnaceae)	Seeds	<i>Digitalis</i> sp., <i>Angelica gigas</i> , <i>Curcuma longa</i>	Korea	2009	KR20090131938	Stress, sleep disturbance, antioxidant
<i>Valeriana officinalis</i> (Valerianaceae)	Roots	<i>Origanum</i> sp., <i>Thymus</i> sp., <i>Hypericum perforatum</i> , <i>Inula helenium</i>	Russia	2009	RU20090132033	Stress, sleep disturbance, antioxidant
<i>Morinda citrifolia</i> (Rubiaceae)	Roots	Alone	China	2009	CN20091162467	Antidepressant
<i>Astragalus</i> (Leguminosae)	Roots	<i>Arctium lappa</i> , <i>Polygonatum</i> sp., <i>Rehmannia</i> 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
<i>Galphimia glauca</i> (Malpighiaceae)	Aerial parts	Alone	Mexico	2009	MX20090007792	Insomnia, short memory, dizziness and tinnitus, palpitation
<i>Ziziphus jujuba</i> (Rhamnaceae)	NR	Jujuboside, saponins of lily, <i>Polygonum</i> sp., pilose antler, <i>Epimedium</i> sp., <i>Zingiber officinale</i> , glycyrrhizic acid	China	2009	CN20091067127	Relieving stress
<i>Camellia sinensis</i> (Theaceae)	Leaves	<i>Theanine</i> , <i>Panax</i> sp., or <i>Sasamorpha</i> sp.	Korea	2009	KR20090030428	Stabilize arterial pressure, contributes to cessation of retrosternal pain, depression, and insomnia
<i>Valeriana officinalis</i> (Valerianaceae)	Roots	<i>Crataegus</i> sp., <i>Leonurus cardiaca</i> , <i>Inula helenium</i> , <i>Glycyrrhiza uralensis</i> or <i>Glycyrrhiza glabra</i> , <i>Hypericum perforatum</i> , <i>Papaver</i> sp.	Russia	2008	RU20080150453	Promoting sleep, relieving stress
<i>Ziziphus jujuba</i> (Rhamnaceae)	Seeds	<i>Platycladus orientalis</i> , <i>Pueraria</i> sp., <i>Smilax glabra</i> , <i>Prunus persica</i> , <i>Panax ginseng</i>	China	2008	CN20081236792	

<i>Sceletium tortuosum</i> (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
<i>Morus alba</i> L. (Moraceae)	Leaves	Alone	Korea	2008	KR20080083509	Preventing coronary artery diseases, hyperlipidemia, degenerative arthritis, melancholia
<i>Ginkgo biloba</i> (Ginkgoaceae)	Leaves	Alone	Japan	2008	WO2008JP60477	Antidepressant activity
<i>Gardenia jaiminoides</i> (Rubiaceae)	Fruit	Alone	China	2008	CN20081016679	Preventing and/or curing depressive anxiety
<i>Bupleurum</i> (Apiaceae)	Roots	<i>Cyperus</i> sp., <i>Citrus medica</i> , <i>Poncirus trifoliata</i> , <i>Gentiana lutea</i> , <i>Sinapsis alba</i> , <i>Acorus calamus</i> , <i>Rehmannia</i> sp., <i>Albizia julibrissin</i> , <i>Polygonum multiflorum</i> , <i>Ziziphus jujuba</i> , <i>Polygala</i> sp., <i>Coptis</i> sp., <i>Glycyrrhiza glabra</i>	China	2007	CN20071015237	
<i>Erythrina mulungu</i> (Fabaceae)	Hydroalcohol extract	Alone	Brazil	2007	MX20070004690	Dysphoria
<i>Ziziphus jujube</i> (Rhamnaceae)	Seeds	Alone	China	2007	CN20071053859	
<i>Matricaria recutita</i> (Asteraceae)	NR	<i>Salvia</i> sp., <i>Bidens</i> sp., <i>Urtica</i> sp., <i>Rosa</i> sp., <i>Vaccinium</i> sp., <i>Eucalyptus</i> sp., <i>Tanacetum</i> sp., <i>Achillea</i> sp., <i>Calendula</i> sp.	Russia	2006	RU20060145809	Correcting human psychoemotional state for the purpose of removing feelings of aggression, despair, reserve, depression
<i>Bupleurum falcatum</i> (Apiaceae)	Water extract	Alone	Korea	2006	KR20060094166	Inflammatory liver diseases, asthma, arthritis, diabetes, depression, vasodilation, vomiting, pain
<i>Valeriana officinalis</i> (Valerianaceae)	Roots	<i>Proanthocyanidin</i> , vitamins E, B ₃ , B ₆ , B ₁₂ , L-theanine, magnesium	US	2006	US20060413648	Sleep disorders, reduction of stress
<i>Cinnamomum</i> (Lauraceae)	Bark	Cinnamaldehyde extract	China	2006	CN20061054874	Dysphoria, depression, neurasthenia
<i>Valeriana wallichii</i> (Valerianaceae)	NR	Alone	China	2005	CN20051021662	Dysphoria
<i>Salix</i> (Salicaceae)	NR	Alone	Germany	2004	WO2004EP14780	Antidepressant, neuroleptic, tranquilizer, sleeping disorders
<i>Eschscholzia californica</i> (Papaveraceae)	NR	<i>Valeriana officinalis</i>	France	2004	FR20040012531	Tranquilizer, hypnotic
<i>Cinnamomum coccisia</i> (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
<i>Piper methysticum</i> (Piperaceae)	NR	Theobromine	US	2004	US20040945108	Fatigue, muscle tension, nervous depression, headache, obesity, and mild pain, as well as enhancement of cognition and mental focus
<i>Piper methysticum</i> (Piperaceae)	NR	With one or more anxiolytics	US	2004	US20040945106	NR
<i>Piper methysticum</i> (Piperaceae)	Piper methysticine—free extract	Alone	Germany	2004	DE200410039012	Tranquilizer
<i>Scutellaria lateriflora</i> (Lamiaceae)	Standardized extracts	Alone	US	2004	US20040852660	Insomnia, convulsions, muscle tension, spasm
<i>Cnidium officinale</i> (Apiaceae)	Rhizomes	Alone	Korea	2004	KR20040114525	Antispasmodic and preventing hypertension
<i>Nelumbo nucifera</i> (Nelumbonaceae)	Seeds	<i>Rehmannia glutinosa</i> , <i>Pachyma hoelen</i> , <i>Perilla frutescens</i>	Japan	2004	JP20040039362	NR
<i>Anemarrhena asphodeloides</i> (Liliaceae)	Rhizome		Korea	2004	KR20040114532	Antipyretic and hypoglycemic action
<i>Leonurus cardiaca</i> (Lamiaceae)	Alcohol extract	<i>Melissa officinalis</i> , <i>Rosa</i> sp., <i>Echinacea purpurea</i> , <i>Grataegus</i> sp.	Russia	2003	RU20030136406	Sedative
<i>Panax</i> (Araliaceae)	NR	Alone	Korea	2003	KR20030070249	NR
<i>Glycyrrhiza uralensis</i> (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
<i>Griffonia simplicifolia</i> (Fabaceae)	Seeds	Extract of plants rich in 5-hydroxytryptophane	Spain	2002	ES20020002936	Syndromes related to fatigue, including pain, muscular problems, depression
<i>Scutellaria lateriflora</i> (Lamiaceae)	NR	Alone	US	2002	WO2002US29309	Insomnia, convulsions, muscle tension, spasm
<i>Hypericum perforatum</i> (Hypericaceae)	NR	Magnesium asparaginate, <i>Rhodiola rosea</i> , <i>Coffea arabica</i> , flower pollen, <i>Theobroma cacao</i>	Russia	2002	RU20020120352	Nervopsychic stress, fear
<i>Hypericum perforatum</i> (Hypericaceae)	NR	Acetyl-L-carnitine in combination with hypericin	Italy	2000	US20000719551	Nervous alteration due to an anxious state, irritability, or depression
<i>Ginkgo biloba</i> (Ginkgoaceae)	Leaves	Alone	Bulgaria	2000	BG20000104970U	Memory, senile dementia, vertigo, headache, depression, migraine, neuralgia, sexual potency, strengthening of the immune system, atherosclerosis

<i>Hypericum perforatum</i> (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 Stress
<i>Piper methysticum</i> (Piperaceae)	<i>Passiflora</i> sp., <i>Matricaria</i> <i>chamomilla</i> , <i>Humulus</i> <i>lupulus</i> , <i>Schisandra</i> sp. Magnesium salt, <i>Eschscholzia</i> <i>californica</i>	US	1998	US19980102165	NR
<i>Crataegus oxyacantha</i> (Rosaceae)	Cross-linked cellulose carrier	France	1996	FR19960000553	Tension and restlessness
<i>Piper methysticum</i> (Piperaceae)	Increased bilobalide content	Germany	1995	EPI9950100411	Antidepressant
<i>Ginkgo biloba</i> (Ginkgoaceae)		Germany	1994	US19940244900	

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

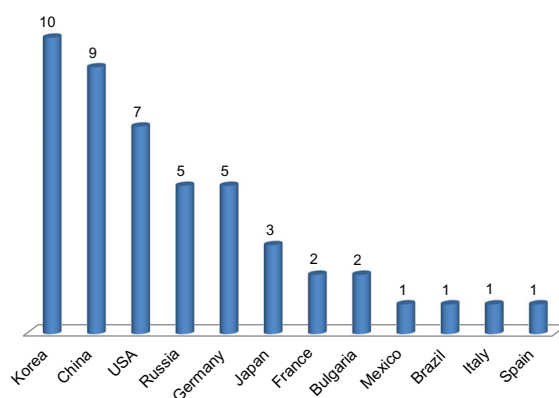


Figure 1 Number of species reported for anxiolytic uses in patents applied for by different countries.

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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