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Article review

Medicinal plants for the treatment of "nervios", anxiety, and depression in Mexican Traditional Medicine

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ABSTRACT

The term "nervios" is referred as a folk illness recognized by Mexican Traditional Medicine, and also widely reported across many countries in Latin America. "Nervios" are characterized by a "state of bodily and mental unrest", which decreases the ability to achieve daily goals. The causes are varied; in fact, any situation that alters the emotional state or mood is interpreted as a possible triggering agent. Depression and anxiety are psychiatric disorders, which share symptoms, or can be included in the same group of disorders with "nervios". The therapies are designed to reassure health, *i.e.* "calm the nerves". For this propose, the oral administration of plants infusions is common. In this review we compile information regarding the plants used for the treatment of "nervios" in México, along with those for which reports of anxiolytic or/and antidepressive activity exist. We found 92 plant species used in folk medicine for the treatment of "nervios", among these, sixteen have been studied experimentally. The most studied plant is *Galphimia glauca* Cav., Malpighiaceae, which current clinical studies have validated its efficacy in patients, and their active components, the triterpenes galphimine A, B, and C, identified. Interestingly only nine plants were found to be reported in folk medicine for the treatment of sadness or/and depression, but their antidepressant activity has not been investigated. However, among the plants used in folk medicine for treatment of "nervios", several, as *Litsea glaucescens* Kunth, Lauraceae, have been proven to show antidepressant activity in experimental models, and some of their active compounds have been determined. These species could be a potential source of compounds with activity in the central nervous system.

Introduction

"Nervios" is a group of human maladies recognized by Mexican Folk or Traditional Medicine, which can be translated as "jitters". Synonyms are: "alteration of nerves, nerves, and nervousness". "Nervios" are characterized by a "state of unrest in which is usual getting insomnia, loss of appetite or compulsive eating, anxiety, rapid pulse, occasional despair and other disorders such as hair loss, dermatitis and weakness. Any circumstances that alter the emotional state or mood are interpreted as possible triggering agents" (Zolla, 1990). Several ethnic groups of México, for instance the "Pame" ethnia at the

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State of San Luis Potosi, distinguish this group of maladies, and name them as "lamayin" (Chemin, 1984).

Several conditions are described as: sporadic, customary, and explosive. The first one is an occasional state suffered by any human being. The second is part of the character of an individual, which in itself is affected, and suffering from a state of chronic anxiety, among other symptoms. The third is a "nervous breakdown", a severe condition, in which the individual shows little control over their emotions and actions, occurring suddenly in response to a stressful stimulus; loss of consciousness may occur (Guarnaccia et al., 1989; Zolla, 1990). The therapies are designed to reassure health, *i.e.* "calm the nerves", recuperate sleep and appetite, and alleviate particular conditions of each case. The oral administration of plant infusions, decoctions, but also as inhalations, as well as hot or cold baths generally prepared with aromatic plant species is common. Massaging, rubbing and kneading the body ("sobadas") are also prescribed for muscle relaxation and to reduce stress. Commonly therapies are accompanied by rituals and ceremonies in order to improve the psychological status (Campos and Cano, 1979; Zolla, 1990)

"Nervios" is referred as a folk illness; it is included in the "culture-bound syndromes", treated in the Appendix I of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (American Psychiatric Association, 1994). This manual defines "nervios" as an idiom of distress used throughout Latin America and the Caribbean, which reflects a broad range of expressions of negative feeling states due to stressful experiences (Alcántara et al., 2012), the phrase is helpful in indicating negative aspects of experiences, and associated culturally shaped communication patters (Durà-Vilà and Hodes, 2012). However, "nervios" is so widely reported across many contrasting regional, linguistic, and demographic barriers that it defies description as a culture-bound syndrome. The way the illness is experienced and conceptualized may vary across cultural groups (Guarnaccia, 1993). "Nervios" may be caused different reasons; in fact, every stressful situation can act as a triggering agent that alters the mood and induces depression or anxiety, for example, familiar, economic and/or working problems, strong impression or a social conflict (Guarnaccia et al., 1996). These individuals may experience a variety of social, political, economic and familiar issues (Weller et al., 2008).

Depression and anxiety are clinic illnesses related to the central nervous system (CNS), which share symptoms, or can be included in the same illness group with the so called "nervios". For example, people who suffer of "nervios" or depression experience sadness, disturbed sleep and reduced concentration and attention (WHO, 2010). In the case of anxiety and "nervios", the people have trembling, dizziness, headaches, stomach disturbances. Mexicans being "ill" with "nervios" or "suffering" from "nervios" report feelings of desperation, emotional condition of restlessness, concentration difficulty, irritability, insomnia and/or feelings of hopelessness, among others. Other health problems may be present, such as loss of appetite or increased appetite, headaches, rapid heart palpitations, and high or low pressure, chest and abdominal pains, tingling sensations, hair loss, dermatitis and/or weakness.

The aim of this paper is to answer the questions: How many and which plant species are reported in Mexican Traditional Medicine for the treatment of "nervios", depression and anxiety? Which species have been studied chemically and pharmacologically? Does scientific evidence support the purported medicinal folk applications for the treatment of nervous illness by the studied plants?

In this review, we compile the plants used for the treatment of"nervios" (Chart 1), sadness and/or depression (Chart 2) in folk medicine in México. The plant species were obtained from bibliographic sources of Mexican Traditional Medicine. A systematic search was performed using the following terms: "nervios", México, plants depression, sadness and anxiety, and their combinations. The review covers the past 15 years until March of 2013, mainly from the electronic data bases: Base de Datos de Plantas Medicinales (BADEPLAM, Instituto de Biología of the Universidad Nacional Autónoma de México), Atlas de las Plantas de la Medicina Tradicional *Mexicana* (Argueta et al., 1994), and Medline (PubMed). We also reviewed those plants subjected to scientific studies, since these species can be a potential source of compounds with activity in the CNS. Biomedical researchers that research the chemical and pharmacological basis of ethnobotanical knowledge, for instance by studying extracts of plants, commonly use animal models to determine potential antidepressant-like or anxiolytic-like activity. This review was divided in the following sections: Plants used in Mexican Traditional Medicine for the treatment of "nervios" (Section 1), or sadness and depression (Section 2). Experimental studies of plants with models to assess anxiolytic activity (Section 3) or antidepressant activity (Section 4).

Medicinal plants in folk medicine for the treatment of "nervios"

In México, the treatments for "nervios" include home remedies, such as herbal "teas" (including infusions and decoctions), are used by rural and urban population. Patients, even in metropolitan areas, can combine traditional medicine practices with prescribed drugs (Campos and Cano, 1979; Finkler, 1989; Argueta et al., 1994). Teas are prepared with only one plant, or as mixture of plants, among them: *Agastache mexicana* (toronjil morado), *Agastache mexicana* subsp. *xolocotziana* (toronjil blanco), *Dracocephalum moldavica* (toronjil azul or chino), *Cinnamonum* sp. (canela), different species of *Citrus* flowers (flor de azahar), *Chiranthodendron pentadactylon* (flor de manita), *Ternstroemia* sp. (tila), *Foeniculum vulgare* (hinojo), *Ipomea stans* (tumbavaquero) (Balam, 1987; Magdaleno, 1987; Campos, 1990; Linares et al., 1995). Cold and hot baths with these plants are recommended, especially with aromatic species (Chemin, 1984; Zavala, 1990).

According to our review, in México, there are 92 plant species used for the treatment of "nervios" (Chart 1). These represents the 2.74-2.96% of Mexican medicinal plants, estimated the order of 3103 to 3352 species (Bye, 1998). These are reports from several locations from 16 of 32 States of the Republic. Almost 50% of the species belong to eight families: Asteraceae 10.87%, Rutaceae 7.6%, Lamiacea 6.52%, Passifloraceae 5.43%,

Chart 1
Summarized information about the plant species used in México for the treatment of "nervios".

Plant	Family	Popular name	Part used	Location	Specific use registered	Reference
Achillea millefolium L.	Asteraceae	Milenrama	Branches	Puebla, Quimixtlán	Against nervios	Chino and Jáqcques, 1986
Agastache mexicana (Kunth) Lint & Epling.	Lamiaceae	Toronjil	All.	Distrito Federal	Nervios illness	Balcazar, 1985; Bye and Linares, 1992; Nicholson and Arzeni, 1993
Annona diversifolia Saff.	Annonaceae	Ilama	Seeds		Analgesic*	González-Trujano et al. 1998
Apium graveolens L.	Umbelliferae	Apio	Roots	Sinaloa, Ahome	Nervios	Marquez-Salazar, 1997
Artemisia ludoviciana Nutt.	Asteraceae	Estafiate	Leaves	Puebla, Valle de Tehuacán-Cuicatlán and Tabasco, Nacajuca	Nervios and mood disorder	Magaña, 2009
Baccharis glutinosa Pers.	Asteraceae	Jarilla	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Buddleja perfoliata Kunth.	Loganiaceae	Salvia de bolita	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Calea zacatechichi Schltdl.	Asteraceae	Zacatechichi	Leaves	Morelos, Tepoztlán	Nervios	Gómez and Chong 1985
Casimiroa edulis La Llave & Lex.	Rutaceae	Zapote blanco	Leaves Bark	Morelos, Tepoztlán; Nuevo León, Monterrey and Morelos, Tepoztlán	As soothing nervios	Azcarraga-Rosette, 2004; Gómez and Chong, 1985; Nicholson andArzeni, 1993
Cecropia obtusifolia Bertol.	Moraceae	Guarumbo	Leaves	Tabasco, Nacajuca	Nervios	Magaña, 2009
Chiranthodendron pentadactylon Larreat.	Sterculiaceae	Flor de manita	Flowers	Chihuahua and Sinaloa, Ahome	Nervios illness	Linares et al., 1990; Marquez-Salazar, 1997
Choisya ternata Kunth	Rutaceae	Naranjo mexicano	Leaves	Puebla	Against nervous	Martínez, 1939
Chrysanthemum sp.	Asteraceae	Crisantemo	Leaves	Oaxaca, Santa María Ixcatlán	Nervios	Rangel-Landa and. Lemus, 2002
Citrus aurantifolia (Christm.) Swingle	Rutaceae	Limón	Flowers Fruits Branches	Puebla, Zapotitlán de las Salinas; Tabasco, Nacajuca; Distrito Federal and Veracruz, Coxquihui	Nervios	Martínez, 1939; Paredes, 2001
Citrus aurantium L.	Rutaceae	Naranja agría	Leaves Flowers Fruits	Tabasco, Nacajuca; Hidalgo, Mineral del Monte, Mineral del chico Morelos, Tepoztlán; Sinaloa, Ahome and San Luis Potosí, San Antonio	Nervios Tranquilizer for nervous person	Alcorn1983; Azcarraga-Rosette, 2004; Cedillo, 1990; Marquez-Salazar, 1997; Martínez, 1939
Citrus máxima (Burm.) Merr.	Rutaceae	Pomelo	Fruit	Sinaloa, Ahome	Nervios	Zamora and Barquín, 1997
Citrus sinensis (L.) Osbeck	Rutaceae	Naranja dulce	Flowers Pericarp Branches	Morelos, Tepoztlan; Tabasco, Nacajuca; Distrito Federal; Michoacán, Ocampo and Puebla	Nervios	Cedillo, 1990; Chino and Jáqcques 1986; Linares et al., 1990

Chart 1 *cont.*

Plant	Family	Popular name	Part used	Location	Specific use registered	Reference
Croton fragilis Kunth	Euphorbiaceae		Bark	Sinaloa, Ahome	Nervios	Marquez-Salazar, 1997
Cymbopogon citrates (DC.) Stapf	Poaceae	Zacate limón	Leaves	Tabasco, Nacajuca	Nervios	Magaña, 2009
Cynara scolymus L.	Asteraceae	Alcachofa	Leaves	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Dianthus caryophyllus L.	Caryophyllaceae	Clavel	Flowers	Sinaloa, Ahome	Nervios	Marquez-Salazar, 1997
Diospyros digyna Jacq.	Ebenaceae	Zapote Negro	Bark	Morelos, Tepoztlán	Nervios	Gómez and Chong, 1985
Dracocephalum moldavica L.	Lamiaceae	Toronjil chino Toronjil azul	Branches	Durango, Durango and Distrito Federal	Nervios	Azcarraga-Rosette, 2004; Bye and Linares, 1992
Ehretia tinifolia L.	Boraginaceae	Roble Beek	Fruits	Snaloa, Ahome	Nervios	Marquez-Salazar, 1997
Eryngium foetidum L.	Apiaceae	Cilantro cimarrón	Roots	Tabasco, Nacajuca	Nervios	Magaña-Alejandro, 2009
Foeniculum vulgare Mill.	Apiaceae	Hinojo	Seeds	Distrito Federal	Nervios illness	Linares et al., 1990
Galphimia glauca Cav.	Malpighiaceae	Calderona Amarilla	Branches Seeds	Distrito Federal	Nervios excitement	Tortoriello and Lozoya 1992
Gelsemium sempervirens (L.) J. St. Hil.	Loganiaceae	Retama	Branches	Morelos	Against nervios	Baytelman, 1982
Guaiacum coulteri A. Garay.	Zygophyllaceae	Guayacán	Buds	Sinaloa, Ahome	Nervios	Marquez-Salazar, 1997
Guazuma ulmifolia Lam.	Sterculiaceae	Guazima	Roots	Tabasco, Nacajuca	Nervios	Magaña, 2009
Haematoxylum sp.	Leguminosae	Palo de Brasil	Flowers	Distrito Federal	Nervios	Torres-Herrera, 1985
Helianthus annuus L.	Asteraceae	Girasol	Steam Seeds	Sinaloa, Ahome and Distrito Federal	Nervios	Marquez-Salazar, 1997
Heliotropium pringlei B.L. Rob.	Boraginaceae		Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Heteropterys beecheyana A. Juss.	Malpighiaceae	Bejuco	Stems	Morelos, Tepoztlán	As soothing nervios	Cedillo, 1990; Gómez and Chong 1985; Huerta-Reyes et al., 2013
Hibiscus sabdariffa L.	Malvaceae	Jamaica	Flowers	Sinaloa, Ahome	Nervios	Marquez-Salazar, 1997
Inodes japa Stand l.	Arecaceae			Yucatán	Nervios	Martínez, 1939
Ipomea stans Cav.	Convolvulaceae	Tumbavaqueros	Roots	Guanajuato, Hidalgo and Puebla	Nervios	Argueta et al., 1994; Rzedowski and Calderón, 1985
Justicia pectoralis Jacq.	Acanthaceae		Branches	Tabasco, Nacajuca	Nervios	Magaña, 2009
Lactuca sativa L.	Asteraceae	Lechuga	Leaves	Tabasco, Nacajuca	Nervios	Magaña, 2009; Marquez-Salazar, 1997
Lepidium virginicum L.	Cruciferae	Lentejilla	Branches	San Luis	Nervios	Martínez, 1939
Lippia alba (Miller) N.E. Br.	Verbenaceae	Salve Real	Branches	Sinaloa, Ahome	Nervios	Marquez-Salazar, G. 1997

Chart 1 *cont.*

Plant	Family	Popular name	Part used	Location	Specific use registered	Reference
Litsea glauucescens Kunth	Lauraceae	Laurel	Leaves	San Felipe del Progreso, Estado de México	Nervios	Hernández, 1959
Loeselia mexicana (Lam.) Bran.	Polemoniaceae	Espinosilla	Leaves Branches	Guerrero, Michoacán, Nayarit, Durango, Zacatecas, Aguascalientes, Guanajuato, among others	Susto*	Argueta et al., 1994
Magnolia dealbata Zuce	Magnoliaceae	Eloxochitl	Bark Leaves	Puebla	Nervios Tranquilizer	Chino and Jacques 1986
Matricaria chamomilla L.	Asteraceae	Manzanilla	Branches	Tabasco, Nacajuca	Nervios	Magaña, 2009
Marrubium vulgare L.	Lamiaceae	Manrrubio	Branches	Distrito, Federal	Nervios	Azcarraga-Rosette, 2004
Melissa officinalis L.	Lamiaceae	Toronjil	Branches	Tabasco, Nacajuca	Nervios	Magaña, 2009
Montanoa frutescens (Mairet) Hemsley	Asteraceae	Zoapatle	Leaves	Morelos y Distrito Federal	Mood disorders*	Carro-Juárez et al., 2012
Musa acuminata Colladon	Musaceae	Plátano	Leaves	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Musa paradisiaca L.	Musaceae L.	Plátano	Leaves	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Ocimum basilicum L.	Lamiaceae	Albahacar	Branches	Distrito Federal and Sinaloa, Ahome	Nervios	Azcarraga-Rosette, 2004; Marquez-Salazar, 1997
Parkinsonia aculeata L.	Leguminosae	Palo verde Bagote	Flowers	Morelos	Against Nervios	Baytelman, 1982
Passiflora coriácea Juss.	Passifloraceae	Ala de murcielago	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Passiflora edulis Sims	Passifloraceae	Maracuyá	Leaves	Michoacán, Pátzcuaro	Nervios	Mapes, 1983; 1985
Passiflora foetida L.	Passifloraceae	Pasiflora	Leaves	Tabasco, Nacajuca	Nervios	Magaña, 2009
Passiflora sp.	Passifloraceae	Pasiflora	Leaves	Morelos, Tepoztlan	To control nervios	Cedillo, 1990
Passiflora subpeltata Ortega	Passifloraceae	Granada cimarrona	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Peumus boldus Molina.	Monimiaceae	Boldo	All	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Piqueria trinervia Cav.	Asteraceae	Hierba de San Nicolás	Leaves	San Luis Potosí	Against nervios	Martínez, 1939
Phalaris canariensis L.	Gramineae	Alpiste	Seeds	Tabasco, Nacajuca	Nervios	Magaña 2009
Phoradendron velutinum (DC.) Nutt.	Loranthaceae	Injerto	Leaves	Morelos, Tepoztlán	To calm nervios tension	Cedillo, 1990
Phyla nodiflora (L.) Greene	Verbenaceae	Té	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Psidium guayava L.	Myrtaceae	Gayaba	Leaves	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Prunus capulí Cav. & Spreng.	Rosaceae	Capulín	Branches	Oaxaca	For nervios weakness	Martínez, 1928
Portulaca oleracea L.	Portulacaceae	Verdolaga	Branches	Puebla, Zapotitlán de las salinas	Nervios	Paredes, 2001.
Pyrus communis L.	Rosaceae	Pera	Flowers	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Pyrus malus L.	Rosaceae	Manzano	Flowers	Distrito Federal	Nervios	Azcarraga-Rosette, 2004

Chart 1 *cont.*

Plant	Family	Popular name	Part used	Location	Specific use registered	Reference
Rhipsalis baccifera (Mill.) Stearn	Cactaceae	Diciplinilla	Steams	San Luís Potosí, San Antonio	Nervios	Alcorn, 1983
Rivina humilis L.	Phytolaccaceae	Bajatripa	Branches	Puebla, Pahuatlan	Nervios	Castro, 1988
Ruta graveolens L.	Rutaceae	Ruda	Seeds	Morelos, Tlatempa	Against nervios	Baytelman B. 1982
Salvia microphylla Kunth.	Labiateae	Mirto	Branches	Distrito Federal	Tranquilizer for babies and for nervios	Azcarraga-Rosette, 2004
Salvia polystachia Ortega	Labiateae	Chía	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Satureja macrostema (Benth.) Briq.	Lamiaceae	Té de monte	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Selaginella pallescens (C. Presl) Spring	Selaginellaceae	Flor de piedra Doradilla	Leaves	Oaxaca, San Pablo Villa de Mitla	Nervios	Messer, 1978
Tagetes lucida Cav.	Asteraceae	Pericón	Branches	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Talauma mexicana (DC.) G. Don	Magnoliaceae	Yoloxóchitl	Seeds	Distrito Federal	Nervios	Martínez-Alfaro et al., 1995
Ternstroemia oocarpa Melch.	Theaceae	Tila	Flowers	Puebla, Quimixtlán	Nervios	Chino and Jáqcques, 1986
Ternstroemia pringlei Standl.	Theaceae	Tila	Flowers	Morelos, Tepoztlán	As soothing nervios	Cedillo, 1990
Ternstroemia sylvatica Schltdl. &Cham.	Theaceae	Flor de tila	Flowers	Distrito Federal and Sinaloa, Ahome	Nervios	Azcarraga-Rosette, 2004; Chino and Jáqcques, 1986
Ternstroemia tepezapote Schltdl. & Cham.	Theaceae	Manglillo Tronpillo	Flowers	Chiapas, San Fernando; Puebla, Quimixtlán and Oaxaca, Santiago Comaltepec	Nervios	Gutiérrez-Miranda, 2003; Martin
Tilia mexicana Schltdl.	Tiliaceae	Tila	Flowers	Tabasco, Nacajuca and Morelos Tepoztlán	Nervios	Gómez and Chong, 1985
Tradescantia spathacea Sw.	Commelinaceae	Zopitolera	Leaves	Tabasco, Nacajuca	Nervios	Magaña, 2009
Triticuma estivum L.	Poaceae	Trigo	Seeds	Distrito Federal	Nervios	Azcarraga-Rosette, 2004
Turnera diffusa (Willd.) ex Schult.	Turneraceae	Damiana	Leaves Branches	Sinaloa, Ahome; Baja California Sur and Morelos, San Juan Texcalpan	Nervios	Baytelman, 1982
Urtica dioica L.	Urticaceae	Ortiga, chichicastle	Branches	Hidalgo, Mineral del Monte	To calm nervios	Zamora and Barquín, 1997
Urtica urens L.	Urtucaceae	Ortiga	Branches	Hidalgo, Mineral del Monte	To calm nervios	Zamora and Barquín, 1997
Valeriana ceratophylla kunth	Caprifoliaceae	Valeriana	Leaves	Tabasco, Nacajuca	Nervios	Magaña, 2009
Valeriana edulis subsp. procera (Kunth) F.G. Mey.	Caprifoliaceae	Valeriana Raíz de gato	Roots	Michoacán; Estado de México	Against nervios	Martínez, 1939
Valeriana officinalis L.	Caprifoliaceae	Valeriana Raíz de gato	Roots	Morelos	Against nervios	Baytelman, 1982; Martínez, 1939
Valeriana sorbifolia Kunth	Caprifoliaceae	Valeriana		Michocán; Estado de México	Against nervios	Martínez, 1939
Verbena litoralis Kunth.	Verbenaceae	Verbena	Leaves	Chiapas, San Fernando	Nervios	Gutiérrez-Miranda, 2003
Viola tricolor L.	Violaceae		Leaves	Distrito Federal	Nervios	Azcarraga-Rosette, 2004

*Reported for an illness related to central nervous system but not for "nervios".

Chart 2
Summarized information about the plant species used in México for the treatment of sadness or/and depression.

Plant	Family	Popular name	Part used	Location	Specific use registered	Reference
Bougainvillea spectabilis Willd	Nyctaginaceae	Bugambilia	Flowers	Puebla, Coxcatlán	Sadness of children	Canales et al., 2005
Chenopodium ambrosioides L.	Chenopodiaceae	Epazote	All	Morelos, Tlatempa	Sadness of children	Baytelman, 1982
Chiranthodendron pentadactylon Larreat.	Sterculiaceae	Flor de manita	Flowers	Distrito Federal	Depression, nostalgia	Azcarraga-Rosette, 2004
Citrus limetta Risso.	Rutaceae	Lima	Leaves	Sinaloa, Ahome. El fuerte	Sadness	Marquez-Salazar, 1997
Cyperus esculentus L.	Cyperaceae	Cebollín	Roots	Oaxaca, Santa María Tecomavaca	Depression	Blanckaert, 2007
Cyperus flavescens L.	Cyperaceae	Paja de guillo	Roots	Oaxaca, Santa María Tecomavaca	Depression	Blanckaert, 2007
Haematoxylum brasiletto Karst	Leguminosae	Palo de brasil	Bark	Chihuahua	Sadness of children	Bye, 1976
Porophyllum macrocephalum DC.	Asrearaceae	Pápaloquelite	Leaves	San Luis Potosí	Depression, anguish	Alcorn, 1983

Valerianaceae 4.35%, Rosaceae 3.2%, Theaceae 2.17%, and Verbenaceae 1.08%. All the plants have a popular name, but it can vary among different locations. Almost all species are prepared as tea from the aerial parts; however, in several cases the roots are used. Seventeen plants are edible, although, not always the eatable part is used medicinally; only three plants are also used as spices or for seasoning. Several species were introduced from Europe, Asia and African after XVI century, the process of importation and the globalization of information have continued, and new plants have been added, such as *Valeriana officinalis*, *Hypericum perforatum*, and *Lavanda* sp.

Medicinal plants in folk medicine for the treatment of sadness and depression

Several ethnobotanical reports explicitly indicate nine plants used for the treatment of depression, or sadness, a symptom of depression (Chart 2). These species belong to eight families. Cyperaceae family includes two species. These reports are from seven different states of the country. Almost all species are prepared as infusions of the aerial parts; however, in two cases roots are used. None of these plants have been studied to validate their purported properties. *Argemone mexicana*, *Chenopodium ambrosoides*, and *Chiranthodendron pentadactylon* are endemic.

Experimental studies of Mexican plants with anxiolytic activity

Anxiety is considered to be a normal reaction to a stressor, characterized as a state of being that arises from general and non-specific stimuli perceived as being potentially threatening in the future. This perception often results in an apprehensive mood accompanied by increased arousal and vigilance, which when taken to an extreme persist for extended periods of time (Dias et al., 2013). However, when anxiety becomes overwhelming, it may fall under the classification of an anxiety disorder. It is interesting to note that over 40% of the culture-bound syndromes listed in Appendix I of DSM-IV explicitly are overlapped with anxiety pathology, and research has focused on the links between these syndromes and anxiety disorders of DSM (Alcántara et al., 2012).

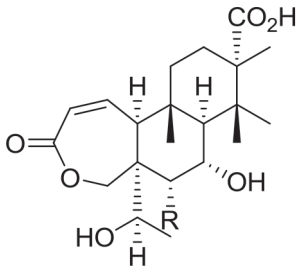
Anxiety in laboratory rodents are often measured using crude behavioral assays, such as the elevated plus maze (EPM). Anxiety can also be modeled using both light-enhanced, and dark-enhanced startle paradigms, context conditioning, and by exploiting the unpredictability of aversive events, such as mild shock (Dias et al., 2013).

Contemporaneously, The use of herbal medicine is widespread amongst suffers of mood and anxiety disorders. Worldwide, species as *Melissa officinalis* (lemon balm), *Matricaria recutita* (chamomile) and *Humulus lupulus* (hops) are known anxiolytics, and its mechanism of action has started to be explored (Sarris, 2011). The species used in México scientifically studied for anxiety models are: *Galphimia glauca*, *Tilia americana* L. var. *mexicana*, *Lippia alba*, *Ipomoea stans*, *Casimiroa edulis*, *Montanoa frutescens*, *Magnolia dealbata*, *Valeriana edulis* ssp.

procera, *Annona diversifolia*, *Matricaria chamomilla* and *Loeselia mexicana*. All, with exception of *M. chamomilla*, *L. alba* and *A. diversifolia*, are species endemic to México. *Lippia alba*, *I. stans*, *V. edulis* ssp. *procera*, *G. glauca*, *M. chamonilla* and *L. mexicana* are herbaceous plants. *Tilia americana* var. *mexicana*, *C. edulis*, *M. frutescens*, *A. diversifolia* and *Magnolia dealbata* are trees. All the above-mentioned species are prepared as infusions of areal parts, with the exception of *V. edulis* ssp. *procera*, for which the roots are used. In these studies, the most used model to assess the anxiolytic activity was the elevated plus maze (EPM); and, almost all experiments used mice as experimental animal, with the exception of *C. edulis* and *M. frutescens* which were tested on rats.

Galphimia glauca *Cav., Malpighiaceae*

Medicinal applications of this species can be tracked to the 16th century (Hernández, 1959); however, its ancient medicinal applications are not related to CNS diseases. Currently, this plant is commonly known as: "calderona amarilla", "flor estrella", "hierba del cuervo", "ojo de gallina", "hierba del desprecio" among others, and is used by the local population as sedative (Argueta, 1994). It is used in the Mexican traditional medicine for the treatment of nervous excitement (Tortoriello and Lozoya, 1992). It is the most studied species for the treatment of anxiety in México and therefore, we present only the most relevant information. Twenty years ago, the sedative activity of the methanolic extract from *G. glauca* was demonstrated in neuropharmacological tests (Tortoriello and Lozoya, 1992). This effect was attributed to a nor-secotriterpene named galphimine B (GB) (**2**) (Tortoriello and Ortega, 1993). Afterwards, galphimine A (**1**) and galphimine E (**3**) were isolated, and found to be active, although less potent than GB. Likewise, the standardized methanolic extract of *G. glauca* (standardized on GB, 8.3 mg/g) administered thrice (24, 18 and 1 h before the test), elicited anxiolytic-like effect (500, 1000 and 2000 mg/kg, *p.o.*) when evaluated in EPM test (González-Cortazar and Tortoriello, 2006). In other study, it was observed that the structural feature responsible for the anxiolytic activity of the compounds was the presence of free hydroxyl groups at C-4, C-6, and C-7, and the double bond in the A ring (Herrera-Ruiz et al., 2006). On the other hand, the effect of the chronic administration of aqueous, ethanolic or methanolic extracts of *G. glauca* (standardized in its content of the three galphimines) was evaluated in mice in order to know their behavioral and pharmaco-toxicological effects. Only a decrease of the spontaneous activity was observed, no deaths were induced and the histopathological analysis of different organs did not show any alterations. The administration of these extracts for 56 days (same doses and route) in mice did not cause any changes in the biochemical parameters for liver function. Also, it was demonstrated that none of the three extracts were genotoxic (Aguilar-Santamaría et al., 2007). The therapeutic effectiveness, safety, and the tolerability of a new standardized herbal medicinal product was next developed from the aqueous extract of *G. glauca* on patients with generalized anxiety disorder in a controlled, randomized, double-blind clinical trial. This herbal product showed important anxiolytic effectiveness, very similar to that observed with lorazepam, and both treatments showed therapeutic safety (Herrera-Arellano et al., 2007). Later, the effectiveness, safety, and tolerability of *G. glauca* herbal product were evaluated by administering it for fifteen weeks to patients with generalized anxiety disorder, using a double-blind, randomized experimental design. The authors concluded that *G. glauca* herbal medicinal product administered for fifteen weeks to patients with generalized anxiety disorder showed greater anxiolytic effectiveness than that obtained with lorazepam, with high percentages of therapeutic tolerability and safety (Herrera-Arellano et al., 2012). Regarding to the mode of action of *G. glauca*, its main active compound, galphimine-B, has been demonstrated to selectively inhibit discharges of dopaminergic neurons in the ventral tegmental area, and to interact with the serotoninergic system of the dorsal hippocampus (Jiménez-Ferrer et al., 2011).

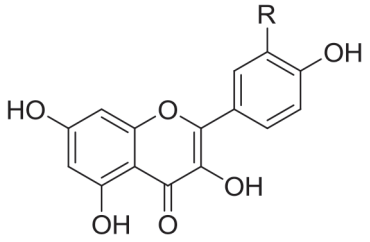


1 R=OH
2 R=H
3 R=OAc

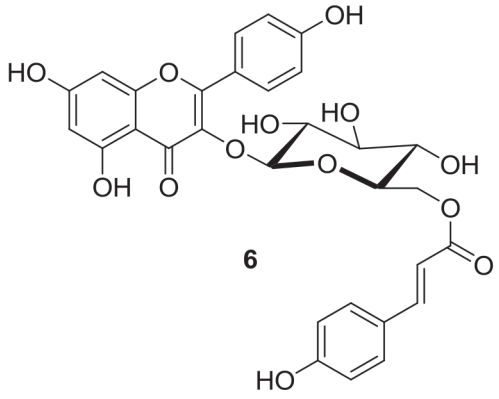
Tilia americana *var.* mexicana *(Schltdl.) Hardin, Malvaceae*

Popularly it is known as "tila", "cirimbo", "sirimo", "tila de bolita", "tsirimu" and "tilo", among others. The aerial parts of this species have been used in Mexican Traditional Medicine for treating "nervous" disorders, insomnia, and headache (Martínez, 1987; Bello, 1993; Argueta et al., 1994). The *n*-hexane (10 and 30 mg/kg, *i.p.*) and methanol (10-300 mg/kg, *i.p.*) extracts of the inflorescences had an anxiolytic-like effect, and at higher doses it produced a decrease in the ambulatory activity (Aguirre-Hernández et al., 2007a). The anxiolytic activity was determined by EPM, hole board test (HBT), and exploratory rearing. Acute toxicity was observed with a lower dose of methanol extract (LD_{50} 375 mg/kg) in comparison with the hexane extract (LD_{50} > 2900 mg/kg). These researchers suggested that the hexane extract elicits a depressant action on the CNS, at least in part by the presence of β-sitosterol (1-10 mg/kg, *i.p.*), and some fatty acids that remain to be identified (Aguirre-Hernández et al., 2007b). The same investigation group collected the inflorescences of Mexican Tilia in three different regions of México in order to compare flavonoid content and anxiolytic-like response. The flavonoid content of the methanol extracts were analyzed by HPLC-MS, although the extracts were prepared differently from those used for pharmacological evaluation. The analysis revealed specific flavonoid composition, demonstrating differences between flowers and bracts depending on the site of collection; differences were due to the sugar residues present, but not in the aglycones, kaempferol (**4**) and quercetin

(**5**) content. To assess the anxiolytic-like response, methanol extracts of Tilia inflorescences (from 10 to 300 mg/kg, *i.p.*) were tested in mice using open-field, hole-board and plus-maze tests, as well as sodium pentobarbital-induced hypnosis. No difference in the neuropharmacological activity was observed between methanol extracts of Mexican Tilia collected in three different places. Nevertheless, quercetin and kaempferol aglycons were tested and showed anxiolytic-like response, therefore the authors suggest that the pharmacological effect of Tilia inflorescences involves quercetin and kaempferol (10 mg/kg, *i.p.*), but is independent of the kind of glycosides present in the samples (Aguirre-Hernández et al., 2010). In contrast, other research group also working with *Tilia americana* subsp. *mexicana* var. *mexicana* and evaluated the anxiolytic effect of four extracts of the combined bracts and flowers, successively macerated with *n*-hexane, ethylacetate, methanol, as well as an ethanol-water extract. These authors reported that hexane, ethyl acetate and aqueous extracts (*p.o.*), displayed no anxiolytic effect, evaluated by EPM test in mice; while the methanol extract at identical doses (25-200 mg/kg) showed anxiolytic effect without motor activity alteration. The methanol extract was subjected to a bioassay-guided fractionation, which afforded a rich flavonoid mixture with anxiolytic activity, identifying tiliroside (**6**) as the major component; however, this compound was not isolated and tested (Herrera-Ruiz et al., 2008). It is noteworthy that other plant species with the popular name "tila" are also used in México for "nervios", but they have been identified as species from the genus *Ternstroemia*. In the case of *Ternstroemia pringlei* the methanol and aqueous extracts from the fruits elicited sedative, but not anxiolytic, activity (Balderas et al., 2008; Lozada-Lechuga et al., 2010).



4 R=H
5 R=OH



6

C**asimiroa edulis** *La Llave & Lex., Rutaceae*

It is a native tree from México, it is widely distributed throughout the central and Southern states. This species has edible fruits, and it is popularly known as "zapote blanco", "matasano", "cochitzapotl", "abache" and "zapote dormilón" (Martínez, 1951). The ancient Nahuatl (the Aztec language) name for the fruits is "zapote"; therefore "cochitzapotl", can be translated in "sleepy fruit" or "sleep-producing fruit" (Lozoya and Enríquez, 1981; Ríos-Castillo et al., 2012). Its uses have been reported to be as tranquilizer, for the treatment of anxiety, and insomnia. The aqueous extract of *C. edulis* leaves showed anxiolytic-like activity (*i.p.*), as determined in EPM test in rats (25-55 mg/kg), but the highest doses (45 and 55 mg/kg) reduced locomotion in open field test (OFT). The aqueous extract action was tested by Forced Swimming Test (FST) but the immobility time wasn't reduced (Molina-Hernández et al., 2004). Other work with this species, evaluated the anxiolytic activities of the hydroalcoholic extract of leaves on male and female rats, as well as on mice. The results revealed that the extract (*i.p.*) caused considerable reduction of locomotor (infrared photocell activity monitor) and exploratory activities (6.25, 12.5, 50 mg/kg) in rats. It also increased the exploration time on EPM open arms (1.56, 3.12 and 12.5 mg/kg) in a similar way to diazepam (1 mg/kg; *i.p.*). In the FST, the extract was as effective as fluoxetine (10 mg/kg; *i.p.*) shortening time of immobility and significantly increasing climbing time (6.25, 12, 25 mg/kg). On the other hand, the extract (*p.o.*) prolonged the pentobarbital-induced hypnosis in mice (1000 mg/kg), increased exploration of the EPM open arms (160 mg/kg), and partially protected the animals from the pentylenetetrazol-induced convulsions (800 mg/kg) (Mora et al., 2005).

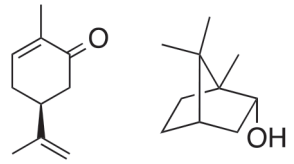
Magnolia dealbata *Zucc., Magnoliaceae*

Its medicinal use was reported since the 16th century (Hernández, 1959; De la Cruz, 1991; Sahagun, 1999). It is an endemic species from México of limited distribution with only six populations in the cloud forests located in the south-central region of this country. A decoction made from its bark and leaves is used in Mexican traditional medicine as tranquilizer, to treat epilepsy (Gutiérrez, 1993) and for "nervios" (Chino and Jacques, 1986). The ethanol extract of the leaves induced a significant and dose-dependent (30-300 mg/kg) decrease in the anxiety response in mice (*p.o.*) in EPM, HBT and exploratory rearing test; the ambulatory activity was also determined in the OFT, but all of tested doses produced a reduction in this behavior. Moreover, *M. dealbata* not only prolonged the time of sodium pentobarbital-induced hypnosis and delayed the onset of pentylenetetrazole (PTZ)-induced myoclonus and clonus, but also hindered the presence of tonic seizures without mortality (Martínez et al., 2006).

Lippia alba *(Mill.) N.E. Br. ex Britton & P. Wilson, Verbenaceae*

Popularly known as "mirto", "pitiona", "salvia de Castilla", "té de Castilla", "salve real" among others, is an aromatic shrub, widely used in Central and South America for the treatment of different clinical conditions, as analgesic and tranquilizer

(Hennebelle et al., 2008). The neuropharmacological profile of the essential oil leaves was determined in rats. It was found that the essential oil had anxiolytic activity administered for fourteen days (12.5 and 25 mg/kg; *i.p.*), using the elevated T-maze (ETM) as experimental model. However, the same treatment, no changes were found in the behavior of rats in the OFT. The monoterpene R-(-)-carvone (25 mg/kg, *i.p.*) (**7**) was identified as its active principle (Hatano et al., 2012). Regarding its mechanism of action, the authors suggested that R-(-)-carvone modulates behavioral inhibition (*i.e.*, avoidance responses) in brain areas such as the amygdala, and the septo-hippocampal system, activated in approach-avoidance conflict situations, for instance when the animal is placed in the enclosed arm of the ETM. This proposal was based on previous reports on the depressant activity of two enantiomers of carvone (de Sousa et al., 2007), and the mechanism of action proposed for other monoterpenesas (+)- and (-)-borneol (**8**) (Granger et al., 2005).

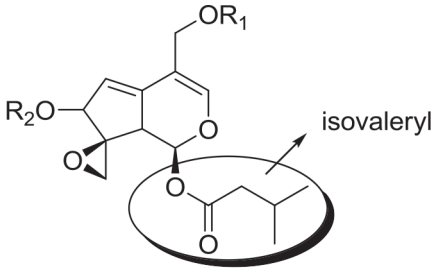


7 **8**

V*aleriana edulis ssp. procera (Kunth) F.G. Mey., Caprifoliaceae*

The underground organs of several species of genus *Valeriana* (Caprifoliaceae) are used by the traditional medicine of many cultures as mild sedative, and tranquilizer, and as a sleep inducing aid (Houghton, 1999). The genus is comprised of about 200 species, and has been used medicinally before Christianity in the Mediterranean area, India, and China. Several species are object of trade, for instance *V. officinalis* (European Valerian), *V. jatamansi* (*V. waliichi*) (India and Pakistan Valerian), *V. fauriei* (Japanese Valerian) (Joshi et al., 2005). In México, the native Valerian species *Valeriana edulis* subsp. *procera* (Kunth) Meyer (=V. *procera* Kunth), is also important in the medicinal plant market, (Oliva et al., 2004; Joshi et al., 2005). Chemical differences have been determined between the European and Mexican Valerian, although both species have similar effects on CNS. A previous report described the sedative and enhanced pentobarbital effect of valerenic acid isolated from *V. officinalis* (Hendriks et al., 1985), but it has been reported that valerenic acid is absent in Mexican *V. edulis* (Castillo et al., 2002), and the valepotriates concentration is higher in comparison with other *Valeriana species* (Bos et al., 1998). Dihydroisovaltrate is the main valepotriate in *V. edulis* hydroalcohol extract (Herrera-Arellano et al., 2001). The content of valepotriates in *V. edulis* root hydroalcohol extract has been estimated in 3.55% (Wagner et al., 1970), A crude ethanol extract of *V. officinalis* root (free of valepotriates) did not have an anticonvulsant effect against PTZ (Hiller and Zetler, 1996), thus, suggesting these compounds play an important role in the anticonvulsant effect of *V. edulis*.

The anxiolytic activity of ethanol extract (70%) of Mexican Valerian roots was assessed in mice using the exploratory rearing as behavioral model. The roots were obtained by a micropropagation method, and the extract showed anxiolytic and anticonvulsant activity at 100, 300 and 1000 mg/kg (*i.p.*). In addition, the extract decreased rotarod performance and traction force, and prolonged pentobarbital-induced sleeping time at the highest dose. The pharmacological effects have been attributed to their valepotriates content, which include valtrate (**9**) and isovaltrate (**10**) as major components (Oliva et al., 2004). The anxiolytic activity of valepotriates has been tested in patients using a mixture of 80% dihydrovaltrate, 15% valtrate and 5% acevaltrate. Thirty-six patients with generalized anxiety disorder (DSM III-R) were randomized after a 2-week wash-out, and assigned one of the following treatments for four weeks (n= 12 per group): 1) valepotriates (mean daily dose: 81.3 mg); 2) diazepam (mean daily dose: 6.5 mg); or 3) placebo. A parallel, double-blind, flexible-dose, placebo-controlled design was employed. The preliminary data obtained from this study suggested that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety (Andreatini et al., 2002). On the other hand, it has been described that valepotriates act in the brain through gamma-aminobutyric acid (GABA) receptors (Ortíz et al., 1999).



9 R_1=Ac, R_2=isovaleryl
10 R_1=isovaleryl, R_2=Ac

Montanoa frutescens *Mairet ex DC, Asteraceae*

"Zoapatle" or "Cihuapatli" (cihua: women; pahtli: medicine) is the Nahuatl name assigned to a group of plants (*i.e.* M. tomentosa, *M. frutescens* and *M. grandiflora*) from the genus *Montanoa*. The aqueous crude extract from these plants has been used for centuries in the Mexican traditional medicine to facilitate child delivery and as remedy of female reproductive impairments, such as amenorrhea (Ríos-Castillo et al., 2012; Béjar et al., 2000), and for mood disorders (Carro-Juárez et al., 2012). Early descriptions about the use of cihuapatli aqueous crude extract describe it as a traditional labor inducing remedy, which is mentioned in the book "Libellus de Medicinalibus Indorum Herbis" written in 1552 (De la Cruz, 1991), where traditional recipes and prescriptions are listed. Additionally, mood and ''nervous'' disorders are treated with the aqueous crude extract of cihuapatli. Ximenez (1615) wrote that ''cihuapatli resolves the mood changes and nerves in an admirable form''. The aqueous extract of *M. frutescens* (50 mg/kg; *p.o.*) showed anxiolytic-like activity in rats on the EPM experimental model, in a similar manner to 2 mg/kg of diazepam, without disruption of general motor activity. The

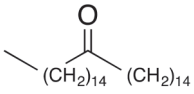
anxiolytic-like effect was blocked by picrotoxin, indicating that GABAA receptors are involved in the modulation of this effect (Carro-Juárez et al., 2012).

Ipomoea stans *Cav., Convolvulaceae*

Root infusions have been used in Mexican traditional medicine for the treatment of epileptic seizures (Díaz, 1976), as anticonvulsant, sedative, purgative, abortive, hypotensor, for renal disorders and headaches; it is popularly known as "tumbavaqueros" ("overthrowing cowboys"), probably due to its effect on the CNS, or its toxic properties at higher doses (Rzedowski and Calderón, 1985; Argueta et al., 1994). The ethyl acetate extract (AcOEt) from the roots of *I. stans* has CNS activity, for instance it has anxiolytic effect in mice (2.5 and 5.0 mg/kg, *i.p.*). At higher doses (20.0 and 40.0 mg/kg), this extract significantly reduced the spontaneous motor activity. Furthermore, at doses of 2.5, 5.0, 10.0 and 20.0 mg/kg, the extract protected mice against PTZ-induced convulsions, and increased the hypnotic effect induced by pentobarbital. Also, ethyl acetate extract was able to increase GABA release in the anterior brain cortex of mice. The extract did not elicit any antidepressant effects on mice exposed to FST (Herrera-Ruiz et al., 2007).

Annona diversifolia *Saff., Annonaceae*

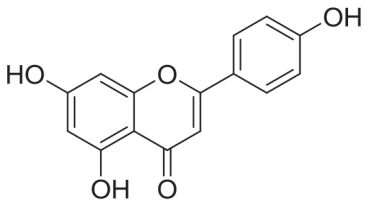
This species is known as the tree of "ilama". It is a tropical fruit tree found in Central America. The native Nahuatl name is "ilamatzapotl" (tzapotl: soft fruit and ilama: old woman; that is "old lady fruit", or "zapote de vieja"). The aim of the study was to investigate the behavioral effects of palmitone (**11**) isolated from *A. diversifolia* in an anti-anxiety response in experimental models in mice. In the EPM test, palmitone administration (0.3, 1, 3, 10 and 30 mg/kg, *i.p.*) lengthened, from 50 to 199%, the time spent in the open arm region of the maze at all doses tested, in comparison to the vehicle group. Palmitone significantly modified rearing activity in the exploratory cylinder in a dose-dependent manner, decreasing the number of rearings with an effective ED_{50} of 0.79 mg/kg. In addition, in the hole-board test, nose-poking was also significantly decreased in a dose-dependent fashion at ED_{50} 9.07 mg/kg. Moreover, palmitone at any dose didn't cause changes in motor activity, or disruption in traction performance. In contrast, diazepam, used as reference drug, produced an anxiolytic effect with a significant and dose-dependent decrease in motor coordination accompanied by disruption of traction performance. Behavioral studies suggest an anti-anxiety effect produced by palmitone but its neuropharmacological profile differs from that observed for benzodiazepines such as diazepam (González-Trujano et al., 1998; 2006).



11

Matricaria chamomilla *L., Asteraceae*

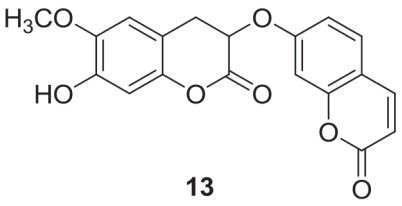
This species is native of Europe and West Asia, but currently is considered a cosmopolitan species. Since its arrival to México during the 16th century, it has been used mainly to treat diseases related with the gastrointestinal system, such as diarrhea (Chino and Jacques, 1986); in other countries the dried flower heads are used in folk medicine to prepare a spasmolytic and sedative tea. The fractionation of the aqueous extract of this plant led to the detection of several fractions with significant affinity for the central benzodiazepine receptor, and to the isolation and identification of 5,7,4'-trihydroxyflavone (apigenin) (**12**) in one of them. Apigenin competitively inhibits the binding of flunitrazepam with a Ki of 4 µM, but had no effect on muscarinic receptors, α1adrenoceptors, and on the binding of muscimol to GABAA receptors. Moreover, apigenin (3 mg/kg, *i.p.*) had a clear anxiolytic activity in mice in the EPM test without evident sedation, or muscle relaxant effects, at doses similar to those used for classical benzodiazepines; furthermore, no anticonvulsant action was detected (Viola et al., 1995). On the other hand a randomized, double-blind, placebo-controlled trial to test the efficacy and tolerability of *Matricaria chamomile* extract therapy was conducted, standardized to a content of 1.2% apigenin (chamomile was prepared as 220 mg capsules), in patients with mild to moderate generalized anxiety disorder (GAD). The results suggested that chamomile may have modest anxiolytic activity in patients with mild to moderate GAD (Amsterdam et al., 2009). Furthermore, this research team examined in a randomized, double-blind, placebo-controlled study, the antianxiety and antidepressant action of oral pharmaceutical-grade chamomile (*M. recutita*) extract, standardized to a content of 1.2% apigenin extract, in patients with symptoms of comorbid anxiety and depression. The authors concluded that chamomile may be clinically relevant due to its antidepressant activity in addition to its previously observed anxiolytic activity (Amsterdam et al., 2012). Another group analyzed one fraction of the methanol extract of the dried flowers of *M. chamomilla* by HPLC-MS-MS, also identified apigenin as a major component. By radioreceptor binding assays, they confirmed the activity of flavonoids on the GABAA receptor. However, when they administered apigenin (0.5-50 mg/kg) *i.p.* in rats, it did not demonstrate anxiolytic, myorelaxant, or anticonvulsant properties, and only reduced locomotor activity (Avallone et al., 2000).



12

Loeselia mexicana *(Lam.) Brand, Polemoniaceae*

Loeselia mexicana, commonly known as "espinosilla", "chuparrosa" or "gallina ciega" is used in Mexican Traditional Medicine to treat fevers, digestive disorders such as dysentery, stomach pain, and swelling, diarrhea, vomiting, and headaches, against dandruff, hair fall, and shock or "susto" (Argueta et al., 1994). The anxiolytic effect of methanol extract was evaluated in mice on the EPM test. The methanol extract was standardized based on its daphnoretin (**13**) concentration (HPLC) and was administered orally for 24, 18, and 1 h prior to the biological tests. It was examined if the anxiolytic effect was due to its interaction with the GABAergic system by administering a GABAA antagonist. The 200 and 400 mg/kg of extract containing 3.14 and 6.28 of daphnoretin, respectively, induced and anxiolytic effect in mice without modification on the spontaneous motor activity. The anxiolytic activity of 200 mg/kg of extract was inhibited by picrotoxin, bicuculline and flumazenil but not by PTZ, the effect that appears to be mediated in part by activation of GABAergic system (Herrera-Ruiz et al., 2011).



13

Experimental studies of Mexican plants with antidepressant-like activity

People who suffer major depression are characterized by deep sadness, anhedonia, low self-esteem, mental slowness, and loss of concentration, among others. The World Health Organization predicts that depression will be the second most prevalent cause of illness-induced disability by 2020. The exposure to trauma and stress are predisposing factors for major depression; for this reason depression is often viewed as a manifestation of the inability to cope with stress. Therefore, many models and tests used to assess depression-related behavior in rodents involve exposure to stressful situations. Of these experimental procedures, the forced swim test (FST) is probably the most widely and most frequently used. A related, but not synonymous task is the tail suspension test (TST), in which a mouse hung upside-down by its tail exhibits passive immobility after several minutes of futile struggling (Cryan and Holmes, 2005). Several drugs are available for the treatment of depression; however due its secondary and adverse effects, the development of new drugs is a continuous endeavor, which includes research of herbal drugs. Some plants have been studied for their potential antidepressant activity. *Hypericum perforatum* is a well-known herbal medicinal treatment, while *Rhodiola rosea* and *Crocus sativus* offer promise for the treatment of depression (Sarris, 2011). Among the species used in México that have been scientifically tested in depression models are: *Mimosa pudica*, *Tagetes lucida*, *Annona cherimola*, *Byrsonima crassifolia* and *Litsea glaucescens*. The first three are herbaceous plants, while the remaining species are trees, all of them popularly used in the treatment of "nervios" (Chart 1), but are not described for the treatment of sadness or/and depression (Chart 2).

Mimosa pudica *L., Fabaceae*

The infusion made from the dried leaves of this species is used to subside human depression (Del Amo, 1979; Mendieta and Del Amo, 1981). In the Oaxaca, Quintana Roo and Veracruz States it is used against insomnia, as somniferous, soporific as a sedative by inhaling the leaves, the stems and the flowers, it can be used recently cut or dried, and it can be used in baths (Avilés, 1985). The aqueous extract administered for a 30-day period (6.0, 8.0 mg/kg; *i.p.*) reduced immobility time of rats in the FST in the same extent as clomipramine (1.25 mg/kg; *i.p.*) and desipramine-HCI (2.14 m/kg; *i.p.*). However, M. pudica did not show any anxiolytic activity when evaluated in the EPM test (Molina et al., 1999).

Tagetes lucida *Cav., Asteraceae*

It is a plant native of México and Central America. In México, it is known as "pericón", "anisillo", "hierba anis" and "hierba de Santa Maria". It is also known as "hierba de San Juan" and sold in substitution of *Hypericum perforatum* (St. John's Wort). *Tagetes lucida* is recommended as stimulant of the immune system, and to treat emotional and nervous complaints, such as anxiety, irritability and depression. The yellow and aromatic flowers are also used as seasoning and as colorant for cooking corn cobs and the fruits of *Sechium edule* (Linares et al., 1995). It has been mentioned as medicinal plant since the 16th century in the Florentine and De la Cruz-Badiano Codices (De la Cruz, 1991; Sahagun, 1999).

The aqueous extract of leaves, flowers and stems of *T. Lucida* was prepared by water decoction for 30 min, presumably following ethnobotanical records. It administered orally (10, 50, 100 mg/kg) for fourteen consecutive days, and evaluated on day 14, 2 h after the last dose treatment; fluoxetine (10 mg/kg, *p.o.*) was used as a positive control. The extract significantly reduced immobility in FST and increased swimming without affecting climbing behavior, suggesting the involvement of the serotonergic system in the antidepressant-like active (Guadarrama-Cruz et al., 2008). These doses were not able to modify neither the motor activity, nor the male sexual behavior. In a subsequent paper the antidepressant activity of different extracts of *T. lucida* was assessed. These extracts were successively prepared in a Soxhlet extractor with hexane, dichloromethane, methanol, and water, and tested at 10 and 50 mg/kg administered (*p.o.*) to rats for fourteen days and evaluated using the FST. The positive control used was fluoxetine (FLX, 5 mg/kg). Only the aqueous extract of *T. lucida* at a dose of 50 mg/kg significantly reduced immobility behavior and increased swimming in the FST, similar to FLX. With respect to the mechanism of action, pretreatment with PCPA, an inhibitor of serotonin synthesis (100 mg/kg/day for four consecutive days), inhibited the antidepressant effect of both *T. lucida* and FLX, indicating that antidepressant-like effect in the FST was mediated by the serotonergic system. Moreover, the aqueous extract (*p.o.*) did not produce lethality or any significant changes in behavior (Gabriela et al., 2012). It is noteworthy that

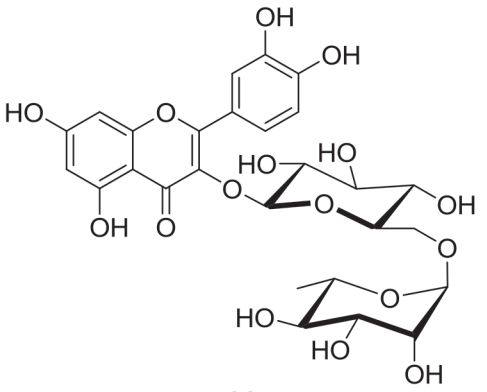
all experiments with *T. lucida* were performed on rats using FST, and this behavior model can suggest the mechanism of action but would require higher quantities of the tested substances, and are more expensive than mice.

Annona cherimola *Mill., Annonaceae*

Since the 16th century Francisco Hernández related the medicinal use of this species, as indicated by the following description: "the decoction of the bark, applied as drops in the eyes or the ears, is said to remove the pain of headache, teeth and eyes" (Hernández, 1959). Currently several species of Annona are used due to their anxiolytic properties (Martínez-Vázquez et al., 2012). The alkaloid extract of the leaves of *Annona cherimola* was prepared and administered to mice (*i.p.*) three times (24, 7, 1 h), before being tested by FST. The extract produced antidepressant activity in FST at 10 and 20 mg/kg. This effect was not related to the increase in locomotor activity of mice when evaluated in OFT. Several compounds were identified by HPLC-MS in the extract: liriodenine and three aporphine products; 1,2-dimethoxy-5,6,6a,7-tetrahydro-4Hdibenzoquinoline-3,8,9,10-tetraol, anonaine and nornuciferine. None of these compounds were isolated and tested (Martínez-Vázquez et al., 2012).

Byrsonima crassifolia *(L.) Kunth, Malpighiaceae*

Byrsonima crassifolia is a tropical tree widely distributed in México, it also grows abundantly in several regions of Central and South America. It bears edible fruits commonly sold in popular markets. The fruit is popularly known as "nanche," it has a unique flavor in raw form and it is prepared in candies, sweet alcoholic beverages and popsicles. *Byrsonima crassifolia* was cited in Francisco Hernández's "History of the Plants of New Spain" (Hernández, 1959) under the Nahuatl name "nantzinxocotl", (this name includes two terms: xocotl, meaning acid fruit, and, nantzi; mothers or old women), that is xocotl of the mothers or old women. An ethnobotanical survey of medicinal plants conducted by the Mexican Social Security Institute (IMSS) in the state of Oaxaca, México, revealed that *B. crassifolia* was among the ten most frequently mentioned plants used by traditional healers to treat gastrointestinal disorders, especially diarrhea and dysentery (Béjar et al., 2000). It has also been used for the treatment of some mental-related diseases (Maldonado, 2008). While studing the gastrointestinal properties of *B. crassifolia*, rats injected intraperitoneally with alcoholic extracts from bark and leaves of this plan exhibited a dose-related decrease in motor activity, mild analgesia, back tonus, enophthalmos, reversible palpebral ptosis, catalepsy (awake) and hypothermia. The demonstrated *in vivo* effects suggested the presence of phytochemicals with mild CNS depressant, antihypertensive and hypothermic effects, which could be beneficial as mild tranquilizers and to reduce fever. Bark extracts were found to be less potent than leaf extracts (Béjar and Malone, 1993). Further studies demonstrated that the methanol extract of aerial parts of *B. crassifolia* elicits a significant antidepressant effect in the FST of mice at a 500 mg/kg dose (*p.o.*). However, it does not possess anxiolytic, sedative, or anticonvulsant properties, and does not cause a reduction of locomotion in mice. The authors identified several flavonoids from this extract by HPLC, such as rutin (**14**), quercetin (**4**) and hesperidin, which are known to have effects on CNS, and therefore may be involved in antidepressant effects. Also, the extract could be considered as relatively safe, toxicologically speaking, with no deaths of mice when orally administered at a dose of 2000 mg/kg (Herrera-Ruiz et al., 2011).



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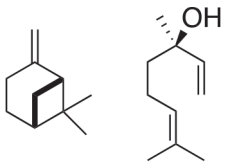
Litsea glaucescens *Kunth, Lauraceae*

Hernández (1559) wrote about a plant named ''Ecapatli'' in Nahuatl. "The natives cure paralysis with its odorous smoke, its decoction administered in washings and baths heals fatigue, and epilepsy of children'', which speaks about its potential activity in the CNS. Currently this plant is known as "laurel" and the leaves are used for food seasoning in the same way as the European Laurus nobilis, also named as "laurel" (Jiménez-Pérez, 2011). The people of the Mazahua ethnia from Atlacomulco, México, prepare a decoction to treat sadness, nervousness, anger, and fright (''susto''); for these purposes they boil the leaves of *L. glaucescens* along with others medicinal plants, such as *Melissa officinalis* (lemon balm), *Mentha* sp. (mint), *Aloysia triphylla* (cedron), and *Cinnamomum zeylanicum* (cinnamon) (Lozano-Mascarua, 1996) (Lozano 222, Herbarium IMSSM). The essential oil of *L. glaucescens* was obtained by hydrodistillation and analyzed by GC/MS. Identification of major compounds was also carried out by comparison with authentic samples. The psychopharmacological profile of *L. glaucescens* essential oil and some its major compounds, were evaluated in mice using several experimental models where the essential oil and active principles were administered i.p: FST, open field test (OFT: Spontaneous locomotor activity), elevated plus-maze (EPM), exploratory cylinder (ECT: sedative-like activity), rotarod (motor coordination) and traction performance (myo-relaxant effect). The essential oil showed antidepressant-like activity at doses of 100 and 300 mg/kg. The monoterpenes β-pinene (**15**) and linalool (**16**) were identified as the two main constituents of the essential oil, and showed antidepressant-like and sedative-like

activities. Eucalyptol, limonene and α-pinene did not elicit antidepressant-like activity, thus, they were not further tested (Guzmán-Gutiérrez et al., 2012).



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Discussion

In México, 92 plant species are used in folk medicine for the treatment of "nervios" (Chart 1), sixteen have been studied experimentally for anxiolytic or antidepressant activity. Regarding their anxiolytic activity, eleven species have been studied scientifically. These figures contrasts with the number of plants used in Mexican Traditional Medicine to treat other diseases, and scientifically investigated; for instance, in the case of respiratory illness, 63 out of 187 species have been tested against Mycobacterium tuberculosis in vitro (Gómez-Cancino et al., 2014). In addition, interest in depression treatment is relatively recent, as well, as the development of animal models to evaluate antidepressant activity (Porsolt et al., 1977), whereas medical interest in infectious diseases and antibacterial asssay development has a long history. In addition, other plant species without ethobotanical reports, or not directly related to "nervios", such as "mood disorders", have also been studied, and their anxiolytic effect demonstrated. The studies were carried out using different extracts prepared from dried plant material, but none was more potent than diazepam (1 mg/kg, *i.p.*), the most common used positive control. However, these extracts at their lowest active doses, do not elicit diazepam´s secondary effects, like sedation or myo-relaxation, which imply an advantage. The most studied plant is *Galphimia glauca*, which current clinical studies have validated its efficacy in patients, and their active components, the triterpenes galphimine A, B, and C, have been identified. *Tilia americana* var. *mexicana* has been studied by two different research groups, both of which coincide that methanol extract is active. In the case of *Galphimia glauca*, *Tilia americana* var. *mexicana*, *Lippia alba*, *Annona diversifolia*, *Matricaria chamomilla* and *Valeriana edulis* ssp. *procera*, their active principles have been identified. There is a great chemical diversity among the isolated compounds such as: triterpenes for *G. glauca* (galphimines); flavonoids for *T. americana* var. *mexicana* (quercetin and kaempferol glycosides, tiliroside) and *M. chamonilla* (apigenin); iridoid triesters of *V. edulis* ssp. *procera* (valtrate and isovaltrate), a derivate of palmitic acid for *A. diversifolia* (palmitone); and the monoterpene carvone for *L. alba*. Therefore, the anxiolytic activity is not exclusive of one kind of compound, and the mechanisms of action may be different. Anxiety is a complex illness that can imply the alteration of performance of different anatomical structures of brain; this entails that there are different targets on which drugs can act against the disease, similar to the way synthetic compounds as benzodiazepines that act through GABAA receptor or buspirone that acts as partial agonist of 5HT1A receptors. Due to the different isolated compounds, or compound mixtures, is not possible to compare their potency due to the different experimental conditions tested. The ED_{50} was calculated only for palmitone isolated from *A. diversifolia* in two different anxiolytic models (*i.p.*) (González-Trujano et al., 2006). The range of anxiolytic activity of *T. americana* active components were: β-sitosterol 1-10 mg/kg, *i.p.* (Aguirre-Hernández, et al., 2007a), quercetin and kaempferol 10 mg/kg, *i.p.* (Aguirre-Hernández et al., 2010); for carvone identified from *L. alba* essential oil was 25 mg/kg, *i.p.* In the case of *Matricaria chamomilla*, the active component, apigenin, was active in mice at 3 mg/kg, but not in rats (Avallone et al., 2000), in both cases administered *i.p.* All *in vivo* studies were tested using an *i.p.* administration route, which eliminates the absorption process through the gastrointestinal system. In the case of *Casimiroa edulis*, *Montanoa frutescens*, *Magnolia dealbata* and *Ipomea stans* the anxiolytic activity of extracts was reported, but no attempt to isolate or identify the active compounds was carried out. The most active was the EtOAc extract of *I. stans* (*i.p.*), and the next was the aqueous extract of *M. frutescens* (*p.o.*). For these two species the mechanism action was suggested. The scenario previously exposed indicates that a lot of work is still needed to complete the pharmacology profiles of these species. A different case is *G. glauca*, the most promissory phytodrug for the treatment of anxiety in México.

Interestingly the plants reported for the treatment of sadness or/and depression (Chart 2) have not been tested for antidepressant activity. However, other plant species used or not in folk medicine for the treatment of "nervios" (Chart 1) have been studied scientifically and their antidepressant activity reported. Different extracts were prepared from these species, and in all cases administered more than once; this is a logical procedure, since nowadays any antidepressant drug needs more than a single administration to show its effect, one disadvantage of antidepressants is the time it takes to show such effect. The experimental protocols vary between three administrations to daily administrations, this makes comparison not feasible, since doses, and route of administration vary. *Mimosa pudica*, *Annona cherimolla*, and *Litsea glaucescens* extracts were administered by *i.p.* route which deliver the active component quickly to the central nervous system. We can stand out that for aqueous extract of *Mimosa pudica* elicited activity at the lowest active doses obtained (6.0 and 8 mg/kg, *i.p.*) administered for a 30-day period, while for *Byrsonia crassifolia* the higher dose (500 mg/kg, *p.o.*) was administered five times before showing activity. Only in the case of *Tagetes lucida* the serotonergic mechanism of action of the aqueous extract was suggested, which is one of the targets of antidepressant drugs. For the essential oil of *Litsea glaucescens*, β-pinene and linalool (100 mg/kg, *i.p.*) were identified as the active principles. The monoterpenes are the major constituents of essential oils, and some of them have shown activity on the central nervous system, for instance (+)-pulegone also significantly increased the latency of convulsions as assessed by the pentylenetetrazole (PTZ) method (de Sousa et al., 2011) and α-terpineol is an analgesic

to mice (Quintans-Júnior et al., 2011). It would be interesting to assess the antidepressant activity of linalool and β-pinene by inhalation tests, since aromatic plant species and compounds have been proven to elicit their activity by this route, it is also know that aromatherapy is a valuable option for the treatment of depression and anxiety (Thachil et al., 2011).

Conclusion

"Nervios" is a folk illness intimately related to stress and psychological distress, and with psychiatric disorders, especially mood and anxiety disorders. In México, it is reported that people who suffer this type of disorder show depressive symptoms in comparison with healthy persons. Medicinal plants were reported effective in the treatment of different health problems, among them "nervios". The chemical and pharmacological study of plants with potential activity in the central nervous system started 25 years ago in México. However, there are few research research groups in this area; available scientific scientific information is low compared to the number of medicinal species of plants reported in this review for "nervios". The efforts should be directed towards the isolation and characterization of active principles. Furthermore, detailed analysis of the active constituents of natural drugs should be directed towards clinical relevance. The isolated active compounds described in this review are of different chemical nature, mainly triterpenes, monoterpenes and flavonoids. The standardization of methods of extraction is essential to maintain reproducible biological activity; since potency can vary due to genetic variation, growing conditions, timing and method of harvest, exposure to air, light, moisture, and type of preservation of the plant materials.

A number of drugs are available for the treatment of depression, but clinical evaluation of these drugs has shown relapse incidence, side effects, and drug interaction. This has been the rationale for the development of new antidepressants, which include herbal drugs. The study of plants with potential effect on the CNS has flourished, especially preclinical in vitro and *in vivo* studies validating phytomedicines, especially for the treatment of depression and anxiety. These studies have provided evidence of beneficial therapeutic activity over the last decades.

Authors´ contribution

SLG-G participated in data collection and writing of the manuscript. All the authors contributed to the critical reading and final editing of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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