



Mexican medicinal plants with anxiolytic or antidepressant activity: Focus on preclinical research



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ABSTRACT

Ethnopharmacological relevance: Anxiety and depression are considered the most prevalent psychiatric disorders worldwide. In Mexico, the use of medicinal plants to alleviate the symptoms associated with these psychiatric disorders is increasing. However, there is little scientific evidence that validates the efficacy of these plants. This evidence needs to be critically revised, and further studied to provided scientific support for their use.

Aim of the study: To identify the plants that are used in Mexico for the treatment of disorders related to anxiety and depression, and to review the current preclinical and when available, clinical information of these plants.

Methods: We searched in scientific databases (Pubmed, Web of Science, Scopus and other web sources such as “Biblioteca digital de la medicina tradicional Mexicana”) for Mexican plants used for the treatment of anxiety and depression that have been analyzed in preclinical studies. Additional information was obtained from published books. For this review, we also consider those plants used in Mexican traditional medicine for the treatment of “nervios,” “susto” or “espanto,” common terms that describe symptoms related to anxiety and depression disorders.

Results: The bibliographic search identified 49 plants used in Mexican traditional medicine for the treatment of disorders related to anxiety and depression. From all these plants, 59% were analyzed in preclinical research, and only 8% were tested in clinical studies; only a few of these studies tried to elucidate their mechanism of action. In general, it is proposed that the plant extracts interact with the GABAergic system. However, only part of these studies attempted to analyze other neurotransmitter systems. Finally, in some cases, drug-herbal interactions were reported.

Conclusions: There is a large number of Mexican medicinal plants used as a treatment for anxiety and depression disorders. Although some of these plants have been studied in preclinical research, in most cases these studies are preliminary, and the understanding of the mechanism of action is inconclusive. The need for systematic studies in preclinical and clinical research is evident, and efforts should be done to fulfill these research. Finally, it is important also to study possible drug-herbal interactions to establish specific recommendations for people that use these plants as anxiolytic or antidepressant treatments either alone or in combination with another type of medicine.

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1. Introduction

Anxiety and depression disorders are currently among the most prevalent psychiatric disorders worldwide (Griebel and Holmes, 2013; Somers et al., 2006). Benzodiazepines (indirect GABA_A receptor agonists) and selective serotonin reuptake inhibitors (SSRIs)

are the drugs of choice for the treatment of anxiety (Griebel and Holmes, 2013). SSRIs are also commonly used to treat depressive disorders (Sharp, 2013). However, the chronic use of benzodiazepines produces tolerance, and a treatment disruption can induce an abrupt withdrawal syndrome (Hood et al., 2014). On the other hand, chronic use of SSRIs can produce considerable side effects (Graf et al., 2014). Therefore, the search for new compounds with anxiolytic and antidepressant properties with less potential to produce adverse effects continues.

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Mexico is a country with a very diverse flora, and many of its indigenous cultures have an extensive pharmacopeia of medicinal plants, knowledge that has been passed through generations. During the last few years, there has been a revival of popular interest in plants used for the treatment of different illnesses including anxiety and depression disorders (Heinrich et al., 1998a). For example, recently, a survey conducted in Mexico City reported an increased use of alternative medicine among people with psychiatric disorders, such as anxiety (Berenzon et al., 2009). It was observed that when people suffer emotional distress, 52.5% practice self-care and 28.2% look for alternative (traditional) medicine.

Nowadays there is little information or research on the use and management of Mexican medicinal plants. A thorough scientific validation of the efficacy of medicinal plants would guarantee the reliability of their usage and also it would help to identify those plants that are ineffective (García-Alvarado et al., 2001).

The present article reviews the existing data on specific plants that are being used in Mexico for the treatment of anxiety- and depression-related disorders. For this purpose, information on Mexican plants with antianxiety/antidepressant effects was obtained from scientific databases (Pubmed, Web of Science, Scopus and other web sources such as “Biblioteca digital de la medicina tradicional mexicana”) and specialized books. In this review, we consider those plants that are reported in Mexican traditional medicine to be used for the treatment of anxiety, or the terms “nervios,” “susto” or “espanto”.

“Nervios” and “susto” are common terms used in Mexican traditional medicine to describe symptoms related to anxiety and depressive disorders. The “Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition” (DSM-5) describes “nervios” as a “state of vulnerability to stressful life experiences and challenging life circumstances” (APA, 2013). Some of the symptoms are irritability, sleep difficulties, nervousness and inability to concentrate. Some related conditions in DSM-5 are general anxiety disorders, social anxiety disorder, major depressive disorder, persistent depressive disorder, among others (APA, 2013).

On the other hand, the DSM-5 describes “susto” (“fright”) as “a cultural description of distress and misfortune among Latin people from Mexico, Central America, and South America”. The associated symptoms are appetite disturbances, inadequate or excessive sleep and feelings of sadness. In this case, some associated conditions in DSM-5 are major depressive disorder, posttraumatic stress disorder and other specific or unspecific stressor-related disorders (APA, 2013). “Espanto” is also related to fright and sometimes is considered synonymous to “susto,” the main difference lies in a religious significance that the different ethnic groups give to the meaning. Usually, “espanto” is an event in which the soul is lost, and with “susto” there is no loss of soul (Castaldo, 2004).

Because the expressions “nervios” and “susto” include symptoms linked to depressive disorders, in this review we also indicate when a plant has been studied in preclinical research for its antidepressant-like effects.

Table 1 lists the plants that are currently being used for the treatment of anxiety, depression, “nervios”, “susto” or “espanto” (anxiety- and depression- related disorders) and have been studied in preclinical research. A short description of the preclinical studies that have been reported for each plant is presented in Section 2.

Table 2 lists the chemical compounds reported for the plants cited in the present review. It also describes the active compounds with anxiolytic or antidepressant activity in preclinical studies. Finally, this table shows other uses reported for the chemical compounds isolated from each plant.

2. Preclinical studies of Mexican plants currently used for the treatment of “anxiety- and depression-related disorders”

2.1. *Achillea millefolium* L

Achillea millefolium L. (Asteraceae) is commonly known in Mexico as “Milenrama,” “Mil-en-rama,” “Mil hojas,” “ciento en rama” or “plumajillo” (Calderón and Rzedowski, 2001). It has been used for centuries in traditional medicine in different countries (Chandler et al., 1982). In Mexico, the infusion of the plant’s aerial parts is used to treat stomach ache, diarrhea, vomit and as an analgesic (García-Alvarado et al., 2001; Alonso-Castro et al., 2012). It has also been used as a tonic for “nervios” (Heinrich et al., 1998b).

In preclinical studies, the hydroalcoholic extract from the aerial parts *Achillea millefolium* L. induced anxiolytic-like effects in the elevated plus-maze and marble-burying tests. These actions were observed after acute or chronic (25 days) treatments.

Flumazenil (a benzodiazepine receptor antagonist) blocked the effects of *A. millefolium*. However, flunitrazepam binding was unaffected (Baretta et al., 2012). Also, in female rats, anxiolytic-like effects of an aqueous extract of the flowers of *A. millefolium* were observed (Molina-Hernández et al., 2004a). These effects vary according to the estrous cycle phase (Molina-Hernández et al., 2004).

2.2. *Agastache mexicana* (Kunth.) Link et Epling

Plants from the genus *Agastache* (Lamiaceae) are aromatic, herbaceous and perennial. They grow in Southeast Asia and North America; in Mexico, there are 12 endemic species (Calderón and Rzedowski, 2001; Lint and Epling, 1945; Martínez-Gordillo et al., 2013). *Agastache mexicana* (Kunth.) Link et Epling is cultivated in the states of Hidalgo, Mexico, Morelos, Puebla, Veracruz and in Mexico City (González-Trujano et al., 2015). This plant is used for the treatment of rheumatism, stomach pain, and hypertension. Also, it is used as tranquilizer and sleep inducer (Argueta et al., 1994; Estrada-Reyes et al., 2014; Linares et al., 1995). Inflorescences are mainly used to alleviate pain while aerial parts are used for their sedative activity (González-Trujano et al., 2015).

In Mexico, there are two subspecies of *Agastache mexicana*: *Agastache mexicana* ssp. *mexicana* and *Agastache mexicana* ssp. *xolocotziana*. Both subspecies are known as “toronjil” and they are used in Mexican traditional medicine for the relief of “susto” and “nervios” conditions (Estrada-Reyes et al., 2014). These two subspecies are phenotypically distinguished by the shape of the leaves, the color of the flowers, and their flavor. However, there is no usage preference between them among the population (Santillán-Ramírez et al., 2008).

A. mexicana ssp. *mexicana* is commonly known as “toronjil morado” (purple or red hyssop) and *A. mexicana* ssp. *xolocotziana* as “toronjil blanco” (white hyssop). In the state of Puebla, the Otomí indigenous population recognizes the two subspecies as “tama,” “toroji,” or “toronjil.” The Tepehua’s, native culture in the states of Veracruz, Hidalgo, and Puebla, named the two subspecies as “pinkil” (Zolla, 1994).

In preclinical studies, the effect of the aqueous extracts of the two subspecies of *Agastache mexicana* (ssp. *mexicana* and ssp. *xolocotziana*) were analyzed. Both subspecies reduced the anxiety-like behavior in a similar way to diazepam, being the second more potent. Authors did not report toxic effects, suggesting that the consumption of these *Agastache* species does not involve significant health risk (Estrada-Reyes et al., 2014).

Also, the methanolic extract of *A. mexicana* and the flavonoid tilianin (the main compound obtained from the plant extract) reduced anxiety-like behavior in mice subjected to the open field,

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