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Revisión | Review

Clinopodium mexicanum: potential and difficulties for the sustainable use of a Mexican medicinal plant

[*Clinopodium mexicanum*: potencial y dificultades para el uso de una planta medicinal mexicana]

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Abstract: *Clinopodium mexicanum* (Benth.) Govaerts (Lamiaceae) is a native plant of Mexico. This plant is used in traditional Mexican medicine for the treatment of cultural specific syndromes such as "susto", "nervios" or "espanto", conditions related to anxiety and depression. In addition, it has a high biocultural value for its medicinal and culinary use and for its exchange value in various indigenous areas of México. This review aims to compile updated information about the ethnobotanical, phytochemistry and commercialization aspects of *Clinopodium mexicanum*, and it focuses on the potential use of this species as a raw material in the phytopharmaceutical industry for the treatment of anxiety and pain. Moreover, it would be a viable productive alternative for many rural communities, which could not only produce the raw material but who could also add value to the sale of the plant.

Keywords: Hill's hyssop; Traditional Mexican medicine; Traditional uses; Phytochemical; Neoponcirin.

Resumen: *Clinopodium mexicanum* (Benth.) Govaerts, es una planta nativa de México. Es usada en la medicina tradicional mexicana para tratar síndromes de filiación cultural como "susto", "nervios" o "espanto", los cuales están asociados a la ansiedad y depresión. Además, la planta presenta un alto valor biocultural por sus usos: medicinal, culinario y por el valor de cambio que tiene en áreas indígenas de México. La revisión presentada tiene como objetivo compilar información actualizada sobre aspectos etnobotánicos, fitoquímicos y comercialización de *Clinopodium mexicanum*. Igualmente señalar el potencial uso de esta especie como materia prima para la elaboración de productos para la ansiedad y el dolor por parte de la industria fitofarmacéutica. Además de ser una alternativa productiva para muchas comunidades rurales, las cuales pueden venderla como materia prima o como producto derivado.

Palabras clave: Toronjil de monte; Medicina tradicional mexicana; Usos tradicionales, Fitoquímica; Neoponcirina.

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INTRODUCTION

Mexico's biological and cultural diversity is widely recognized. This has allowed setting up a complex network of interrelations between people and nature which has resulted in great bio-cultural richness that has in turn generated abundant traditional knowledge. Medicinal uses of native plants stand out among the most important knowledge which has been organized and registered in the Mexican pharmacopoeia (FEUM, 2015). However, many plants used in traditional Mexican medicine are not found in the pharmacopoeia because they lack the necessary scientific studies. Such is case of *Clinopodium. mexicanum*. Currently, traditional therapies have generated interest in the population, who seek alternative treatments giving rise to alternative and complementary medicine. This has encouraged research on ethnobotany, phytochemistry and plant pharmacology used in traditional Mexican medicine. However, research on the production and management of medicinal plants in Mexico is still scarce.

Medicinal plants production has been recognized as a tool for the conservation of biodiversity and the livelihood of rural communities (Phondani *et al*., 2010). Moreover, medicinal plants production is an activity that allows both ecological and sustainable productive activity. In addition, it is an agricultural alternative for small producers who cannot compete in other agricultural sectors. On the other hand, there is a growing demand for medicinal plants; according to the World Bank's estimation, by 2050 the world market for medicinal plants will be approximately 3 trillion dollars (Kala, 2015).

The present review is about *Clinopodium mexicanum* (Lamiaceae), a native plant used in traditional Mexican medicine. It is focused on indicators of this plant's potential as a raw material for the phytopharmaceutical industry, so a systematic research of scientific studies on the biological, ethnobotanical, phytochemical, pharmacological and production aspects of the species was carried out in order to identify what else needs to be researched for the achievement of such objective. For this purpose, databases of peer-reviewed scientific articles were consulted via the Internet using Google Scholar, Pubmed, Scopus, Science Direct and Dialnet, as well as online sources such as the "Digital library of traditional Mexican medicine" and repositories. A comprehensive, systematic review was done using the keywords "*Clinopodium mexicanum"*, "*Satureja Mexicana"* and combinations of these with ethnobotany, traditional Mexican medicine, treatment for "espanto" and "susto", and phytochemical. The abstracts were reviewed, and the entire text was read when warranted.

Taxonomic circumscription of Clinopodium mexicanum

Clinopodium mexicanum was first described in 1840 by Bentham as *Gardoquia mexicana* (Basonym). Later in 1896 Briquet included the genera *Clinopodium, Calamintha, Xenopoma, Gardoquia, Rizoa* and *Micromeria* within the genus *Satureja* (Epling & Játiva, 1966). Finally, the *Satureja* species with American distribution passed to the genus *Clinopodium* and therefore *Satureja mexicana* was renamed by Govaerts in 1999 as *Clinopodium mexicanum* (Harley & Paucar, 2000). The genus *Clinopodium* (Lamiaceae) is in the subtribe Menthinae, tribe Mentheae of the subfamily Nepetoideae (Dumortier) Luerssen (Drew & Sytsma, 2012; Zahra & Shinwari, 2016).

Taxonomic description of Clinopodium mexicanum

C. mexicanum is an aromatic shrub (Figure No. 1) whose stem is covered with trichomes; it has ovate leaves with serrated or serrulate margin leaves. The margins revolute and are as long as 1 cm. It has solitary flowers in the armpits of the upper leaves. The calyx measures up to 6 mm in length and it is shaped like a tube with 13 evident veins and with a ring of hair inside, and the apex is divided into five small ones. The corolla is red or orange with a tubular shape and measuring 2.2 to 3.4 cm in length. It is slightly arched, extending towards the apex (Figure No. 2), and divided into two lips; the upper lip is erect and the inferior is divided into three lobes. It has four stamens, two of which are longer. Style divided in the apex into two somewhat uneven branches (Standley, 1922; Epling & Játiva, 1966).

Distribution and ecology

Clinopodium mexicanum is a species native to Mexico, located in the states of Chiapas, Guanajuato, Guerrero, Hidalgo, Jalisco, Oaxaca, Puebla, Querétaro, San Luis Potosí and Veracruz (Villaseñor, 2016; Cadena, 2017). It is frequently distributed in limestone rocks, in an altitude ranging from 1700 to 2600 m.a.s.l. It is found mainly in regions of sub-humid temperate climate and to a lesser extent in regions of sub-humid climates. It is distributed in regions with precipitation intervals of 400 to 1500 mm and

where the annual average temperature ranges from 14 to 20ºC. It is found in a wide range of vegetation types: xerophytic scrub, microphyllous scrub, secondary vegetation of *Quercus* forests, *Juniperus* forest, *Pinus* forest. It is mainly found in soils of the Leptosol and Cambisol calcaric types, with high stoniness (Magallán *et al*., 2015).

Figure No. 1
Shrubby habit of *Clinopodium mexicanum*

Figure No. 2
Color and form of the flower of *Clinopodium mexicanum*

Ethnobotanical Background
Traditional uses of genus Clinopodium

According to Martinez-Gordillo *et al*. (2013), Mexico has 14 species of *Clinopodium*, of which 10 species are endemic: *C. amissum* (Epling et Játiva) Harley, *C. ganderi* (Epling) Govaerts, *C.*

hintoniorum (B.L. Turner) Govaerts, *C. jaliscanum* (McVaugh et R. Schmid) Govaerts, *C. macrostemum* (Moc. Et Sessé ex Benth.) Kuntze, *C. maderense* (Henr.) Govaerts, *C. mexicanum* (Benth.) Govaerts, *C. micromerioides* (Hemsl.) Govaerts, *C. palmeri* (A. Gray) Kuntze, and *C. procumbens* (Greenm.) Harley. Some species are used with medicinal purposes and for beverage preparation, such as the *C. macrostemum* (Moc. & Sessé ex Benth.) Kuntze, whose aqueous infusion is used to relieve stomach pain in the state of Oaxaca. (Villa-Ruano *et al*., 2015).

Traditional uses of Clinopodium mexicanum

Clinopodium mexicanum is used in traditional medicine as a tranquilizer, for digestion and as an analgesic (Aguilar *et al*., 1994; García, 2000; Quattrocchi, 2012; Domínguez-Vázquez & Castro-Ramírez, 2015). The decoction of the *C. mexicanum* is used to treat gastrointestinal and female reproductive ailments (Nambo, 2015). It is also used for the preparation of aperitif and digestive drinks due to its pleasant taste (García-Hernandez, 2014; Nambo, 2015). *C. mexicanum* is commonly named "poleo", "poleo verde" "toronjil de monte" (hill's hyssop), "toronjil de menta" (mint's hyssop) (Estrada-Reyes *et al*., 2010; López-Rubalcava & Estrada Camarena, 2016). "Toronjil" is a common denomination usually associated to *Melissa officinalis*. However, in Mexico this denomination is related to three species: *Dracocephalum moldavica* "toronjil azul", *Agastache mexicana* "toronjil morado" y *Clinopodium mexicanun* "toronjil de menta". The Otomí ethnia and mestizos called "toronjil" to plants used to treat "susto", "espanto" and "nervios" (Aguilar *et al*., 1994; Santillán-Ramirez *et al*., 2008; Martínez-Vázquez *et al*., 2012; Estrada-Reyes, 2014).

In Oaxaca *C. mexicanum* is known as "hierba de borracho" (Drunken Grass), name which refers to its effect on stomach discomfort caused by the intake of alcoholic beverages (Nambo, 2015), and "chipito" (García-Hernández, 2014; García-Hernández *et al*., 2015). The decoction of its aerial parts is administered as enema to treat constipation, and this decoction can also be drunk to treat stomach ailments; the macerations are used as a topical anesthetic for rheuma (García- Hernández, 2014; García-Hernández *et al*., 2015). The Mixtec name is "*ita'nduku*" and its chocholteco name is "*kaxrhíngaka*", however, the translation for these terms is unknown (García-Hernández, 2014). There are no references of *C. mexicanun* in the mexican herbal pharmacopoeia, which is a document by Mexico's Ministry of Health that sets out general methods of analysis that are used in the preparation of medicines and herbal remedies (FEUM, 2015)

Traditional management

C. mexicanum is considered a species with a high bio-cultural value, and its collection and storage are common in the areas where it grows wild. This value determines the species' high demand in the national, state and district markets, having a high-risk index in some regions of the center of the country (Arellanes *et al*., 2013), although *C. mexicanum* is not included in the NOM-059-SEMARNAT-2010 list of Mexican plants that are at risk (SEMARNAT, 2010). The continuous extraction of wild populations causes their genetic erosion and puts the species at potential risk. For example, a study conducted in the Valley of Tehuacan (State of Puebla) considers that *C. mexicanum* has a high risk index. This risk index considers the economic and cultural value and the management plan of the species; thus, a high-risk index implies a high cultural and economic value and the lack of a management plan (Arellanes *et al*., 2013). The resulting erosion in wild populations has led to the need to grow the plant in some indigenous areas, where small productions are established for self-consumption purposes in "solares", vegetable gardens and small plots (Frei *et al*., 2000). However, even today, harvesting in the wild is the most common practice to obtain native medicinal plants and their products (Rangel-Landa *et al*., 2016), due to which it is inferred that the management of the *C. mexicanum* is rudimentary. An example of this is how the indigenous propagate *C. mexicanum*: the procedure consists of obtaining cuts or transplanting the complete plant from the semi-natural habitats to the plots. In addition, they believe that when they produce the plant it loses its properties, so they mention that they cultivate it as an "experiment" and not as a more accessible alternative to obtain it (García-Hernández, 2014).

On the other hand, the FAO has pointed to medicinal plants as a resource that contributes to people's health and sustainable development (Marshall & Howthorne, 2012). In the case of poleo it can be a productive alternative for farmers of the semi-desert regions, since it is adapted to drought conditions, especially in the semi-desert areas where it shares habitat with other species with medicinal and aromatic use. It can also be a productive alternative in regions with environmental and socioeconomic impact such as

those of the state of Oaxaca.

It is important to note that *C. mexicanum* was used to obtain a patented cultivar named USMINT2 whose commercial name was "Pink Sensation" (USPP1679OP2). The cultivar was obtained by deliberate hybridization between *Clinopodium mexicanum x Hesperozygis* sp. by Sakasaki in Japan (1999). The characteristics of this cultivar are an erect and branched plant with leaves that smell of mint and with light red flowers. It differs from *C. mexicanum* in the respect that it presents greater vigor and a longer duration of the flowers. Another difference is that the flowers have a light red coloration. (Sakazaki, 2006).

Traditional commercialization

In Mexico, there are two markets that have influenced the marketing dynamics of medicinal plants: the Sonora market in Mexico City and the Ozumba tianguis, located in Ozumba de Alzate, state of Mexico. The Sonora market is the main distribution center of medicinal plants from Mexico and abroad, while Ozumba is one of the peripheral markets that supply fresh medicinal plants to the Sonora market. The influence of these markets has generated an increase in the cultivation of plants that are not distributed in the region and those that were only used for family and local consumption (Linares-Mazari & Bye, 2016), and they have fostered commercial relationships with local markets (Villamar, 2016). In Mexico there are other types of commercialization besides mercantile exchange; there is also barter. This type of exchange is common in weekly markets in some regions of the state of Oaxaca (Bye & Linares, 1983; Villamar, 2016). The plants are harvested from the wild and in a few cases they are produced in the plots. Aerial parts of *Clinopodium mexicanum* are sold in local markets (Molina-Luna & Cancino, 2016).

Phytochemistry

According to the bibliography, the first approaches to the phytochemistry of *Clinopodium mexicanum* were carried out by Leyva, 1978, whose work consisted in determining the characteristics of the mint oil extracted from *C. mexicanum,* and comparing them with those of the commercial mints oils (Leyva, 1978). The objective of the research was to find alternatives to reduce the imports of menthol and peppermint essential oil. The Poleo essential oil has the following characteristics: menthyl acetate (34.3%), menthol (4.2%), menthone (42.5%), pulegone (5.5%) and limonene (13.5%). A later study reported that the major compounds of the essential oil were pulegone, piperitone and d-carvone (Hernández, 2003).

The genus *Clinopodium* is characterized by the presence of triterpene compounds such as ursolic acid and its isomer, oleanolic acid, as well as by the presence of rosmarinic acid (Viturro *et al.*, 2000). Likewise, they have free and glycosylated flavonoids (Opalchenova & Obreshkova, 1999; Fernández *et al*., 2006).

The aqueous extract was analyzed using High Resolution Liquid Chromatography. The test detected eleven metabolites of the flavonoid type. Only five metabolites were isolated and structurally identified: 8-hydroxy-salvigenin, 5-demethoxybicylin, neoponcirine, naringenin and hesperidin (Gallegos-Solis, 2008). The high-performance liquid chromatography-mass spectrometry technique identified flavanone glycosides: neoponcirine, poncirin and isonaringin. The flavones 8-hydroxy-salvigenin and gardenina B were identified, as well as the flavonones naringenin and 4-O-methylnaringenin (Estrada-Reyes, 2015). The compounds neoponcirin, poncirin, isonaringenin, hesperidin, 8-hydroxysalvigenin, naringenin, b-sitosterol, ursolic acid and daucosterol have been isolated from *C. mexicanum* (Estrada-Reyes *et al*., 2010; Estrada-Reyes, 2015; Tepe & Cilkiz, 2016). These compounds are found in other medicinal plants and their biological activity has already been determined (Table No. 1).

Pharmacological activity

C. mexicanum is used to treat disorders related to anxiety and depression and there is a preclinical study about it (López-Rubalcaba & Estrada-Camarena, 2016). A general activity test of the aqueous extract of *C. mexicanum* was carried out in which the aqueous extract showed to have a depressant effect of the central nervous system (Estrada-Reyes *et al*., 2010; Estrada-Reyes, 2015). In the preclinical studies the extract extended the sleep time induced by sodium pentobarbital, and it also showed anticonvulsant activity (Estrada-Reyes *et al*., 2010).

Toxicity of the aqueous extract

According to the Lorke methodology, the aqueous extract of *C. mexicanum* was slightly toxic. The mean lethal dose (LD_{50}) was 2154 mg / kg (Gallegos-Solis, 2008; Estrada-Reyes *et al*., 2010). In addition, doses greater than 1600 mg/kg caused

adverse effects (Estrada-Reyes *et al*., 2010). Death of mice occurred at a concentration of 2900 mg/kg (Gallegos-Solis, 2008).

Table No. 1
Bioactivity of the compounds found in *Clinopodium mexicanum*

Name	Group	Sub-group	Bioactivity	References
Neoponcirin	Flavonoid	Flavones	Anxiolytic or antidepressant actions in animal models	Estrada-Reyes *et al*., 2010 Cassani *et al*., 2013
Poncirin	Flavonoid	Flavanone	Potential use for treatment and/or protection of gastritis Improve bone mass and microarchitecture in glucocorticoid-induced osteoporosis	Kim *et al*., 1999; Lee *et al*., 2009; Yoon *et al*., 2012; Kang & Kim, 2016
Isonaringenin	Flavonoid	Flavanone	Antihypertensive effect. Treatment of bronchial asthma	Reshef *et al*., 2005 Funaguchi et al., 2007
Hesperidin	Flavonoid	Flavanone	Antioxidant, anti-inflammatory and antimicrobial activity. Prevention of cardiovascular diseases Radioprotection	Pradeep *et al*., 2008; Hosseinimehr *et al*., 2009; Morand *et al*., 2011; Hou *et al*., 2012; Roohbakhsh *et al*., 2015.
Naringenin	Flavonoid	Flavanone	Gastric anti-ulcer activity Hypocholesterolemic and cardioprotective. Hepatoprotective Antidepressant-like action	Parmar, 1983; Jeon *et al*., 2007; Yi *et al*., 2014; Hermenean *et al*., 2014
β-sitosterol	Terpenes	Triterpenoid	Anti-carcinogenic Anti-atherogenic induces apoptosis human breast cancer cells.	Li *et al*., 2001; Awad *et al*., 2003; Maguire *et al*., 2003; Muti *et al*., 2003; Saeidnia *et al*., 2014.
Ursolic acid	Terpenes	Triterpenoid	Antitumor activity Antioxidant activity	Liu, 2005; Oh *et al*., 2007; Sultana, 2011; Shanmugam *et al*., 2013; Li *et al*., 2017;
Daucosterol	Terpenes	Triterpenoid	Inhibits cancer cell proliferation Promote neural stem cells proliferation	Jiang *et al*., 2015; Zhao *et al*., 2015

Antinociceptive activity

The antinociceptive effect of the aqueous extract was evaluated through the hot-plate acute pain model, and it had an antinociceptive effect on test animals (Gallegos-Solis, 2008; Estrada-Reyes e*t al*., 2010; Estrada-Reyes, 2015). This pharmacological activity may be related to hesperidin (Gallegos-Solis, 2008; Loscalzo *et al*., 2011) and neoponcirin (Estrada-Reyes, 2010), two compounds that have shown analgesic activity (Gallegos-Solis, 2008, Cassani *et al*., 2013). This preclinical study on the antinociceptive effect of neoponcirin showed a thermo-nociceptive effect, which was dose dependent. In addition, neoponcirin had a better analgesic effect on the thermal stimulus than Ibuprofen (Cassani *et al*., 2013). Therefore, neoponcirin has pharmacological potential for the development of analgesics (Estrada-Reyes *et al*., 2010).

Anxiolitic activity

Neoponcirin (2 (*S)*-neoponcirin) is a flavanone rutinoside. This is one of the main compounds obtained from *C. mexicanum* (Estrada-Reyes, 2015). Cassani *et al.* (2013) found that neoponcirin has anxiolytic effects on mice, the anxiolytic-like effect involving the $GABA_A$ receptor. Neoponcirin at low doses (1-10 mg / kg) showed anxiolytic activity as did diazepam (0.5 mg/kg) (Cassani *et al*., 2013).

On the other hand, it is estimated that 43% of those suffering from anxiety use some form of complementary therapy, and among these, herbal treatments are the most popular (Ernst, 2006; Sarris *et al*., 2011). Similarly, the research on herbal medicine in psychiatry has increased by 50%, especially regarding the treatment of depression, anxiety, and insomnia. Although there are medications available to treat these conditions, phytotherapeutic intervention may be beneficial in the treatment of anxiety (Mehta *et al*., 2016). *C. mexicanum* has a high potential use as a phytotherapeutic treatment for anxiety and in the cosmetic industry to make relaxing and anti-stress products, such as massage oils, creams and gels, among others.

Potential application

The richness of the traditional knowledge of plants provides what's necessary for the development of entrepreneurial companies (Kala, 2015) who could offer phytopharmaceutical, nutraceutical and cosmetics' raw materials for the established industry (Garrity, 2004; Kala, 2009). The cultivation of medicinal plants arises as an adequate alternative to satisfy the large-scale demand from the pharmaceutical and phytopharmaceutical companies, which require raw materials that can guarantee content and quality in the final products (Hishe *et al*., 2016). The European Union and the USA are the most important importers of medicinal plants as raw material to produce pharmaceutical products, nutraceuticals, dyes, and products for the phytosanitary control of plants in organic systems (Lubbe & Verpoorte, 2011).

DISCUSSION

The market for natural products is constantly growing; there has been an increasing demand for plant-based products worldwide, which has made the pharmaceutical and food industries to focus their interest on the traditional knowledge of different cultures to find new compounds and foods. The traditional Mexican medicine is a source of new products and compounds for the natural products' industry. The sustainable use of native medicinal plants is the main challenge, for which reason a technological management approach which focuses on the raw material's production and quality should be adopted (Palma-Tenango *et al*., 2017).

According to this review, research efforts are required to take advantage of the potential of *C. mexicanum*. For example, there is a lack of basic information on the species' management aspects such as propagation, genetic variability, phytochemical variability and ecophysiology. These aspects are important to obtaining good quality seeds and for the domestication of the plant. On the other hand, the identification of difficulties allows to develop technological responses to overcome them.

Although *C. mexicanum* is used as a tranquilizer and analgesic, few ethnobotanical records were found, so there is no documentation on all the uses that the species has through its geographical distribution, an important lack since cultural diversity has a great influence on the regional use of resources. Likewise, pharmacological studies have focused only on the plant's effect on the central nervous system. There aren't any other biological activities that have explored the flavonoid contents of the plant or the potential use of its essence oil. More knowledge on these areas would contribute to a more complete vision on the potential industrial use of the species;

the current information regarding the species places it as a plant of interest for the development of analgesics and tranquillizers.

The management and production of this species can be considered inexistent, however, this is one of the priority areas to be developed because the current form of exploitation puts it at risk in certain regions of the country. It is also important to remember that the NOM-059-SEMARNAT-2010 has not been updated. While the wild harvest has continued, the environmental deterioration has increased and the change of land use has diminished the agricultural land area. It is also important to consider the socio-economic aspect because the plant can be found in rural areas with profound poverty and migration, in many of which *C. mexicanum* is a livelihood.

Concluding remarks

Studies about ethnobotany, phytochemistry and preclinical validation of the medicinal applications of *C. mexicanum* were found, however, studies on the economic aspects of the species such as the quantities and price of the plants commercialized in the market at national and state levels were not. The lack of research on production aspects such as agro-ecological requirements, propagation protocols, ecotype diversity and technological plans for small, medium and large-scale management and production is also evident.

The potentiality of the species is based on the increased demand for plant-based products to treat anxiety that can be found in health food stores and pharmacies. *C. mexicanum* is considered an example of a medicinal plant that can become a raw material for the phytopharmaceutical industry to produce products to relieve anxiety and stress. Likewise, it is feasible to use it in the cosmetic industry to produce massage oils and gels for relaxing purposes.

This would be a viable productive alternative for rural communities who already produce *C. mexicanum* and who could not only produce the raw material but who could also add value to the sale of the plant, for example, avoiding the loss of essential oils through proper drying techniques of the plant and then with the subsequent packing of the dry plant for sale.

However, research efforts are needed to define the best strategies to achieve the above and to design production plans. These plans and strategies must consider the market's requirements for high-quality, low production cost products, thus improving the value chain of medicinal plants in Mexico.

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