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Lippia alba: an aromatic plant with recognized value in traditional medicine

Lippia alba: una planta aromática con reconocido valor en la medicina tradicional

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Abstract

Lippia alba is an aromatic shrub with recognized medicinal properties attributed mainly to the phytochemical content of its essential oils. It is widely valued in traditional medicine in several South American countries, while in Mexico, despite being widely used, its use and traditional value for local communities has been poorly documented and little is known about its metabolite profile. Due to the remarkable importance of *L. alba*, a documentary review was conducted on its uses in traditional medicine, its bioactive capacity and its relationship with its metabolite profile, for which information was collected through a detailed search in different scientific databases. It was found that *L. alba* has an interesting profile of metabolites, which have been evaluated mainly in its essential oils. Among the most important volatile metabolites are nerol, geraniol, citral, limonellum, -pinene, -myrcene, among others. Regarding non-volatile secondary metabolites, coumarins, quinones, terpene lactones, flavonoids, tannins, etc. have been found. In Latin America, a wide variety of chemotypes have been reported, whose phytochemical composition is a function of genetic variation, geographic distribution and exposure to different soils and climatic conditions. In addition, *L. alba* has bioactive properties such as antioxidant antivity, antiproliferative activity against different cancer cell lines (human lung adenocarcinoma, murine melanoma and leukemia tumor cells), antibacterial properties, decreased anxiety and vasorelaxant effect, among others. In Mexico, it is necessary to make greater efforts in scientific research to characterize the different chemotypes, evaluate their phytochemical profile and biological activity, as well as to document and safeguard the empirical knowledge that has been transmitted from generation to generation about the traditional use of *L. alba*.

***Lippia alba*, Essential oils, Verbenaceae, Medicinal Plants**

Resumen

Lippia alba es un arbusto aromático que posee reconocidas propiedades medicinales atribuidas principalmente al contenido de fitoquímicos de sus aceites esenciales. Es ampliamente valorada en la medicina tradicional en varios países de Sudamérica, mientras que en México, a pesar de ser extensamente utilizada, se ha documentado poco su uso y valor tradicional para las comunidades locales y poco se conoce de su perfil de metabolitos. Debido a la notable importancia de *L. alba*, se realizó una revisión documental sobre sus usos en la medicina tradicional, su capacidad bioactiva y su relación con el perfil de metabolitos, para la cuál se recopiló información mediante una búsqueda detallada en diferentes bases de datos científicas. Se encontró que *L. alba* posee un interesante perfil de metabolitos, los cuales han sido evaluados principalmente en sus aceites esenciales. Dentro de los metabolitos volátiles más importantes destacan el nerol, geraniol, citral, limonelo, α-pineno, β-mirceno, entre otros. En relación a los metabolitos secundarios no volátiles se han encontrado cumarinas, quinonas, lactonas terpénicas, flavonoides, taninos, etc. En América Latina se reporta una amplia variedad de quimiotipos, cuya composición de fitoquímicos está en función de la variación genética, la distribución geográfica y la exposición a diferentes suelos y condiciones climáticas. Adicionalmente, se destaca que *L. alba* posee propiedades bioactivas como antividad antioxidante, actividad antiproliferativa frente a diferentes líneas celulares de cáncer (adenocarcinoma pulmonar humano, melanoma murino y células tumorales de leucemia), propiedades antibacterianas, disminución de la ansiedad y efecto vasorrelajante, entre otras. En México, es necesario realizar mayores esfuerzos en investigación científica para caracterizar los diferentes quimiotipos, evaluar su perfil de fitoquímicos y actividad biológica, así como documentar y resguardar los conocimientos empíricos que se han transmitido de generación en generación sobre el uso tradicional de *L. alba*.

***Lippia alba*, aceites esenciales, Verbenaceae, Plantas medicinales**

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Introduction

Traditional knowledge is considered as "a set of wisdoms and routines that date back to the origin of humanity, preserved and transmitted by generations orally" (Arrazola-Guendulay *et al*., 2018, p. 56). As described by Arrazola-Guendulay *et al*. (2018), traditional knowledge results from an integration into social processes, cultural and ecological conditions and is transmitted through legends, myths, dogmas, field practices, etc. (p. 56).

For several centuries, in what is now known as Mexico, medicinal plants have formed an important part of the cultural background of the pre-Columbian indigenous peoples, continuing through the independent period and reaching the ethnic groups that populate modern Mexico. The knowledge of this flora and its use to treat various diseases affecting the population are part of the knowledge that is empirically transmitted from generation to generation (Palma-Tenango *et al*., 2017, p. 134).

Culturally created biodiversity is the product of a long process of exchange and systematic natural selection. To this are added medicinal plants, which can belong to primary, secondary, semi-cultivated and cultivated vegetation. This extraordinary wealth is not found in other parts of the world. Without the knowledge of the people, this civilizing experience would be lost for Mexico and humanity (Boege, 2008, p. 20).

"*Lippia alba*, belonging to the Verbenaceae family, is an aromatic shrub native to Latin America, from Mexico to the Caribbean and South America, with recognized medicinal properties." (Garcia *et al*., 2017, p. 140). Its phytochemical content and bioactivity have been studied in different Latin American countries, while in Mexico there are very few scientific studies on the subject; however, its value for the treatment of some ailments, such as gastrointestinal ailments, is traditionally recognized.

Currently, in the northwest of the country, particularly at the Universidad Autónoma de Occidente, efforts are being made to evaluate the phytochemical content of extracts and essential oils of *L. alba*, as well as to study the traditional uses of this plant and its medicinal value for local communities, which is expected to be very high. Due to the remarkable importance of *L. alba* in the region, it is relevant to conduct a detailed review of the main research related to the bioactive compound profile and biological activity of *L. alba* in order to compile, synthesise, update and disseminate knowledge about this valuable medicinal plant.

Theoretical framework

"In Mexico, the use of herbs with healing properties is very old" (Heinrich et al., 1998, pp. 1859-1871; Palma-Tenango *et al*., 2017, p. 134) and "until today it has become a common practice. Generally, the leaves or flowers are used, and sporadically, the stem and root, consumed directly, in infusions or other presentations" (Instituto Nacional de Investigaciones Forestales, Agrícolas y Pecuarias, 2020). The National Biodiversity Commission (CONABIO, 1998) "lists between 3500 and 4000 species of medicinal plants regularly used by the Mexican population". "Indigenous peoples use between 5,000 and 7,000 plant species in various cultural activities" (Boege, 2008, p. 21). "Despite the research that has been carried out, in many cases, the active chemical principle related to the beneficial effects attributed to these plants is unknown" (Instituto Nacional de Investigaciones Forestales, Agrícolas y Pecuarias, 2020).

According to McChesney *et al*. (2007), "there is a growing interest in conducting phytochemical, ethnobotanical or biodiversity assessment research on medicinal plants, which has made it possible to exploit their potential and support their traditional use" (p. 2015). "Natural phytochemicals isolated from plants used in traditional medicine are considered a good alternative to synthetic chemicals" (Juiz *et al*., 2015, p. 214). "Plants function as a laboratory for the production of not only primary metabolites that are used as food by humans, but also secondary metabolites of great pharmaceutical importance such as: glycosides, alkaloids, flavonoids, volatile oils, among others" (Kumar *et al*., 2020, p. 3).

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"Globally, 70% of anticancer compounds (Jacobo-Herrera et al., 2016, p. 391) and 75% of drugs to treat infectious diseases come from natural products" (McChesney *et al*., 2007, p. 2015).

Talking about L. alba and its medicinal properties means talking about the essential oils it contains. "Essential oils and plant extracts have been used for centuries in traditional medicine" (Ferraz, *et al*., 2021, p. 1).

Essential oils are defined as products obtained from a natural raw material of plant origin, by steam distillation, by mechanical processes from the epicarp of citrus fruits, or by dry distillation, after separation of the aqueous phase (if any) by physical processes (ISO, 2013).

Method and tools

This research is a documentary review of the uses of *L. alba* in traditional medicine, its bioactive capacity and its relationship with the phytochemical profile. For the compilation of information, a detailed search of scientific articles was carried out in different databases such as Web of Science, PubMed, Science Direct, Elsevier, among others. The search was carried out in English and Spanish using keywords such as *Lippia alba*, essential oil, medicinal plants, traditional medicine, phytochemicals, among others, including publications from 1998 to 2021. Subsequently, relevant scientific articles were selected for detailed analysis.

Results

L. alba has been widely used in traditional medicine in some South American countries (Juiz et al., 2015, p. 214).

The species is consumed fresh, prepared as teas, sweets, extracts, syrups and among other forms. Tea preparations of its leaves, for example, are popularly used as respiratory remedies and in the treatment of gastrointestinal disorders, diarrhea and dysentery and for having tranquilizing, sedative, analgesic and spasmolytic actions (da Silva *et al*., 2018, p. 792; Gimenes *et al*., 2021, p. 1).

"Due to genetic variation, geographical distribution and exposure to different soils and climatic conditions, *L. alba* can produce essential oils with different chemical composition, which generates a classification by chemotypes" (Souza *et al*. 2017, p. 2). The chemical composition and bioactivity of L. alba essential oils have been extensively studied in different regions (Celis *et al*., 2007, pp. 103-105; Santos *et al*., 2016, pp. 1-9; Gimenes *et al*., 2021, pp. 1-14; Juiz *et al*., 2015, pp. 211-217; Reyes-Solano *et al*., 2017, pp. 962-970; Stashenko *et al*., 2013, pp. 192-202). Garcia *et al*. (2017) determined the relative chemical composition of essential oils produced under various environmental conditions and extraction parameters, highlighting among the main components neral, geraniol, geranial, caryophyllene, caryophyllene oxide (pp. 140-148).

Recently, Gimenes *et al*. (2021) determined the chemical composition of the essential oils of eight genotypes of *L. alba*, finding a total of 73 metabolites, of which -pinene, -myrcene, 1,8-cineole, linalool, neral, geranial and caryophyllene oxide were the most abundant compounds among the accessions (p. 1). Nogueira *et al*. (2021) reported the identification of 15 sesquiterpenes representing 95.45% of the extracted *L. alba* essential oil. The main components reported were β-caryophyllene, β-elemene, D-germacrene and δ-cadinene (p. 3). Moreover, "different non-volatile secondary metabolites such as coumarins, quinones, terpene lactones, flavonoids, biflavonoids, tannins, iridoids, phenylethanoid glycosides, phenylpropanoids and triterpene saponins have been quantified in the chemical composition of *L. alba*" (Acero-Godoy *et al*., 2019, p.6). The secondary metabolites of *L. alba* include phenolic compounds. There are few reports on the determination of phenolic compounds and antioxidant activity in *L. alba*. Among them is the work by Chies *et al*. (2013), who reported significant contents of phenolic compounds and antioxidant activity in extracts of *L. alba* collected in Brazil (p. 194). Gomes et al. (2019) reported a seasonal variation in the flavonoid concentration of two chemotypes of *L. alba* collected in Brazil, being predominant in the summer season (pp. 186, 189-191).

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In Mexico, there are very few studies that evaluate the content of phenolic compounds in *L. alba*; among them is the work by Reyes-Solano *et al*. (2017) who investigated the presence of phenolic compounds in the essential oil in terms of antioxidant activity (pp. 962).

The biological activity of *L. alba* extracts, mainly the essential oils, has been studied in countries such as Brazil and Colombia, standing out for its antioxidant, antifungal, antiparasitic and antimicrobial activity, among other properties (Celis *et al*. 2007, pp. 103-105; Santos *et al*., 2016, pp. 1-9). The antiproliferative effect on K562 leukaemia cells of *L. alba* (colombiana) essential oils produced under different growth, collection and extraction conditions has been evaluated, observing that environmental factors significantly affected the concentrations of secondary metabolites, as well as the biological activity of the different oils obtained from the same chemotype. Furthermore, it was shown that the best antiproliferative effect against the tested cells was obtained from the citral chemotype (Garcia *et al*., 2017, pp. 140-148). Junior et al. (2018) evaluated the anxiolytic effect of *L. alba* essential oils in fish, with satisfactory results (p. 49). Table 1 presents some of the studies evaluating the compound profile and biological activity of L. alba essential oils.

In the northern region of the state of Sinaloa, particularly in the municipality of Guasave, *L. alba* is known by the common name of "salvavidas" and is distributed wild and domestically (Figure 1). In this region, the use of *L. alba* in traditional medicine has been observed, mainly for the treatment of gastrointestinal diseases. Local communities have specific knowledge of the medicinal properties of *L. alba*, which is passed on from generation to generation. Considering the above, it is relevant to study in depth the medicinal uses that *L. alba* mexicana has had over time in the municipality of Guasave, mainly used by local people, in order to generate information that will allow, in the future, the use of the plant on a larger scale.

Sample	Type of extract	Metabolites identified	Biological activity/therapeutic effect	Reference
Leaves of L. alba	Essential oil obtained by hydrodistillation	Monoterpenes nerol/geraniol and citral (constitutes 50% of the crude essential oil)	Cytotoxic activity against B16F10Nex2 (murine melanoma) and A549 (human lung adenocarcinoma) cell lines. IC50 values between 45 and 64 g/mL.	Santos et al. (2016), pp. 1-9.
Leaves and inflorescences of L. alba	Essential oil obtained by microwave-assisted hydrodistillation.	Neral, geraniol, geranial, caryophyllene, caryophyllene oxide.	Essential oils of the citral chemotype showed a cytotoxic effect on K562 (leukaemia) tumour cells ranging from 54-95% and IC50 between 13 and 38.8 g/mL and differences in anti-proliferative activity correlated significantly with variations in caryophyllene oxide concentration.	García et al. (2017), pp. 140-148.
Inflorescences, young leaves and mature leaves of L. alba	Essential oil obtained by microwave-assisted hydrodistillation.	Neral, geraniol, geranial, caryophyllene, caryophyllene oxide.	Induction of programmed cell death in Trypanosoma cruzi (haemoflagellate protozoan causing Chagas disease).)	(Moreno et al. (2018), pp. 1-16
Aerial part of L. alba	Essential oil obtained by hydrodistillation	Geranial, p-cymene, neral, geranic acid, carvone, limonene	Antibacterial potential and anti-biofilm against Staphylococcus aureus, a species of recognised clinical interest.	Porfírio et al. (2017), pp. 1-7.
Leaf of L. alba	Essential oil obtained by hydrodistillation	Carvona as the main constituent	They determined that aromatherapy with L. alba essential oils may be useful as a means of counteracting anxiety in a normal population.	Soto-Vásquez y Alvarado-García (2018), pp. 101-107.
L. alba (part of the plant not specified))	Essential oil	Citral	L. alba essential oil and its main constituent, citral, demonstrated a vasorelaxant effect on isolated rat aorta..	da Silva et al. (2018), pp. 792-798.
L. alba (part of the plant not specified))	Essential oil	Citral, geranial, neral, limonene, carvone, gamma terpinene, among others.	Tocolytic activity of L. alba essential oil and its major constituents, citral and limonene, in the isolated rat uterus.	Pereira-de-Morais et al. (2019), pp. 155-159.
Aerial part of L. al (inflorescences, leaves and stems))	Essential oil obtained by hydrodistillation	β-caryophyllene, β-elemene, D-germacrene and δ-cadinene	Antiviral effect against Zika virus and low cytotoxicity. Larvicidal tests showed action of the essential oil against Aedes albopictus larvae.	Nogueira et al. (2021), pp. 1-8.

Table 1 Studies evaluating the profile of compounds and biological activity of *L. alba* essential oils

Figure 1 Aerial part (stem, leaf and flower) of *L. alba* collected in the municipality of Guasave, Sinaloa

Discussion and conclusions

Plants have been used since ancient times for the treatment of diseases. The use of plant metabolite extracts is an alternative for the design of new medicinal and therapeutic products. *L. alba* has an interesting phytochemical profile that has been related to different beneficial effects on human health. Although it is widely used and studied in several South American countries, little research has been done in Mexico regarding its bioactive compounds profile and evaluation of the biological activity of plant extracts.

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However, it is popular knowledge that it has been used traditionally for the treatment of diseases. Its traditional use by local communities in northwestern Mexico is well recognised. Different varieties, chemotypes and genotypes of L. alba have shown great bioactive potential and a wide range of applications. Therefore, it is important to carry out scientific research that provides support and safeguards the empirical knowledge that has been passed down from generation to generation. Ethnobotanical studies are an essential tool in this work. In addition, the determination of phytochemical profiles and biological activity are indispensable for the understanding of the medicinal properties of plants.

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