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Review /Artículo de revisión

Lippia alba essential oil: chemotypes, bioactivity, and importance of its components in medical therapeutics.

Aceite esencial de *Lippia alba*: quimiotipos, bioactividad e importancia de sus componentes en la terapéutica médica.

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ABSTRACT

Essential oils (EOs) have been utilized in healthcare since ancient times. They are extracted from aromatic plants and primarily consist of terpenes and several organic compounds. Pennyroyal (*Lippia alba*) is a member of the Verbenaceae family that contains essential oil (EO) in its glandular trichomes, showcasing diverse properties in medical therapy, with this bioactivity varying according to the assessed chemotype. A review and compilation of scientific information was conducted on the antibacterial, antifungal, anti-inflammatory, and antioxidant properties *in vitro* of the EO from the seven *L. alba* chemotypes recorded from 2010 to the present, using databases such as PubMed, Scielo, Elsevier, and Springer, along with keywords like *Lippia alba*, essential oil, antibacterial activity, and antifungal activity, among others. The review highlights the bioactivity of *L. alba* EO and demonstrates the chemotypes' effectiveness against various human pathogens, along with their anti-inflammatory and antioxidant properties.

KEY WORDS: Essential oil, chemotype, bioactivity, anti-inflammatory, antioxidant, Verbenaceae, *Lippia alba*.

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RESUMEN

Los aceites esenciales (EOs) se han utilizado desde la época antigua en el área de la salud, se extraen de las plantas aromáticas y están constituidos principalmente por terpenos y una gran cantidad de compuestos orgánicos. Poleo (*Lippia alba*) es una planta de la familia Verbenaceae que posee aceite esencial (EO) en sus tricomas glandulares con diversas propiedades en terapéutica médica, dicha bioactividad varía de acuerdo con el quimiotipo. Se realizó una revisión y compilación de información científica de las propiedades antibacterianas, antifúngicas, antiinflamatorias y antioxidantes *in vitro* del EO de los siete quimiotipos de *L. alba* registrados del 2010 a la fecha, en bases de datos como PubMed, Scielo, Elsevier y Springer, utilizando palabras claves como *Lippia alba*, aceite esencial, actividad antibacteriana y antifúngica. La revisión demuestra el impacto de la bioactividad del EO de *L. alba*, así como la efectividad de los quimiotipos contra una gama de patógenos de humanos, así como sus propiedades antiinflamatorias y antioxidantes.

PALABRAS CLAVE: Aceite esencial, quimiotipo, bioactividad, antiinflamatoria, antioxidante, Verbenaceae, *Lippia alba*.

Introduction

Since ancient times, aromatic plants have consistently been used, and their essential oils (EOs) have been employed in medical treatments or as prophylactics (Shanaida & Golembiovska, 2018). These oils are also utilized in the cosmetic, agricultural, food, and veterinary industries (Sharma *et al.,* 2019).

The term "essential oil" (EO) originates from the Latin phrase "*quinta essential"* (Sattayakhom *et al.,* 2023). It refers to the product of enzymatic reactions in plants, serving various functions such as protection against pathogens and environmental factors, as well as attracting or signaling pollinators (Khaw *et al.,* 2017). These oils mainly consist of terpenes, molecules derived from isoprene that can associate with various compounds, including aldehydes, alcohols, ketones, and resins, among others (Stashenko *et al.,* 2004). They are found in the glandular trichomes of leaves and may be transported to other tissues, such as flowers (Parra-Garcés *et al.,* 2010). The diversity and abundance of these metabolites depend on the plant's genetic material, geographic location, and growth conditions (Eguiarte *et al.,* 2018).

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EOs have shown antibacterial (Santos *et al.,* 2016), antifungal (Arango *et al.,* 2015), antioxidant (Louchard & De Araujo*.,* 2019), anti-inflammatory, and antiseptic properties (Goudjil *et al.,* 2019), along with sedative, analgesic, and anticancer activities (Bahmani *et al.,* 2018). EOs have been used in treating human diseases (Manion & Widder, 2017) and serve as a source for drug synthesis; one example is the vitamin A synthesis from citral, obtained from *L. alba* varieties (Mesquita *et al.,* 2017).

The *Lippia* genus belongs to the Verbenaceae family, which comprises approximately 100 genera and about 3,000 species. These plants can appear as shrubs, herbs, or lianas and rarely bear spines (Linde *et al.,* 2016). Their taxonomic classification is shown in Table 1. Typically, they possess irregular flowers, opposite leaves without appendages, and seeds that lack endosperm (Celis *et al*., 2007). According to the record by Delgado *et al.* (2016), the genus comprises around 221 accepted species, of which 50 have been chemically analyzed. This plant family is notable for including numerous species with medicinal properties (Pérez *et al*., 2018). *L. alba* (Mill.) N.E. Brown is one such species, mainly distributed in South America, Central America, and some regions of Africa (Ciccio & Ocampo, 2010). It is known by various common names, such as lemon balm (Brazil), Juanilama (Costa Rica), prontoalivio (Colombia), poleo (Mexico), and hierba Luisa (Venezuela) (Malik *et al*., 2021). It is an ornamental plant that grows as a subshrub, reaching heights of 1 to 1.5 meters, with slender branches that range in color from light brown to whitish. Its petiole measures 0.5-1.3 cm in length and 0.7-1.2 cm in width; it presents axillary inflorescences arranged in a glomerule with a short axis (Albuquerque *et al*., 2018) (Figure 1). The plant has woody stems and hermaphroditic zygomorphic flowers arranged in axillary spikes, lilac, purple, or white, typically 6 mm long and elongated to 8-12 mm, with hairs on the lower part. The fruits are 3 mm long, in the form of a drupe or dry capsule with a dark violet membranous exocarp that splits into two nutlets at maturity. It features a fasciculated taproot up to 25 cm long and is characterized by a mint-like aromatic scent (Parra-Garcés *et al*., 2010).

L. alba is classified according to its chemotypes. The biogeographic distribution of these chemotypes across the Americas and the Caribbean is partly influenced by ecological factors, which is reflected in a region-based classification, however, genetic factors are considered potentially more decisive in determining the composition of its EOs than environmental ones (Blanco *et al*., 2013). To simplify the chemotype distribution, Hennebelle *et al.* (2008) proposed a classification system for the EOs of *L. alba* based on their major components, the biosynthetic pathways of the terpenes present, and seasonal variations, among other criteria. The EOs extracted from *L. alba* are used for a wide range of purposes, including antidiarrheal, anti-inflammatory, analgesic, antibacterial, antiviral, antioxidant, antidiabetic, antifungal, acaricidal, and insect-repellent applications (Mamun-Or-Rashid, 2013; Álvarez *et al*., 2015; Glamoclija *et al*., 2011; Carvalho *et al*., 2017; Perea-Domínguez *et al*., 2022). EOs can inhibit the growth of microorganisms, a property attributed to the lipophilic nature and low molecular weight of their constituents, which enable the EOs to penetrate cell membranes, causing alterations in the structure and function of the microorganism (Machado *et al*., 2014). The primary aim of this review article is to highlight *L. alba*, from the Verbenaceae family, for the diverse activity of its metabolites found in its EO, its chemotypes, and its biological properties that may be harnessed for the benefit of human health.

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Methodology

A semi-systematic or narrative review was conducted to provide a broad overview of the bioactive effects of *L. alba* EOs and their relevance in medical therapeutics, summarize and discuss key findings on the subject. As part of the information search strategy, the databases PubMed, Scielo, Elsevier, and Springer were used, employing keywords such as "*Lippia alba*," "essential oil," "antibacterial activity," "antifungal activity," "antioxidant activity," and "anti-inflammatory activity," among others. Inclusion criteria encompassed articles published between 2010 and the present (2025), in both Spanish and English. A literature evaluation and analysis were performed to select articles with thematic relevance and scientific quality appropriate for this review. The information was then organized thematically by topic or focus. A general diagram of the methodology is presented in Figure 1.

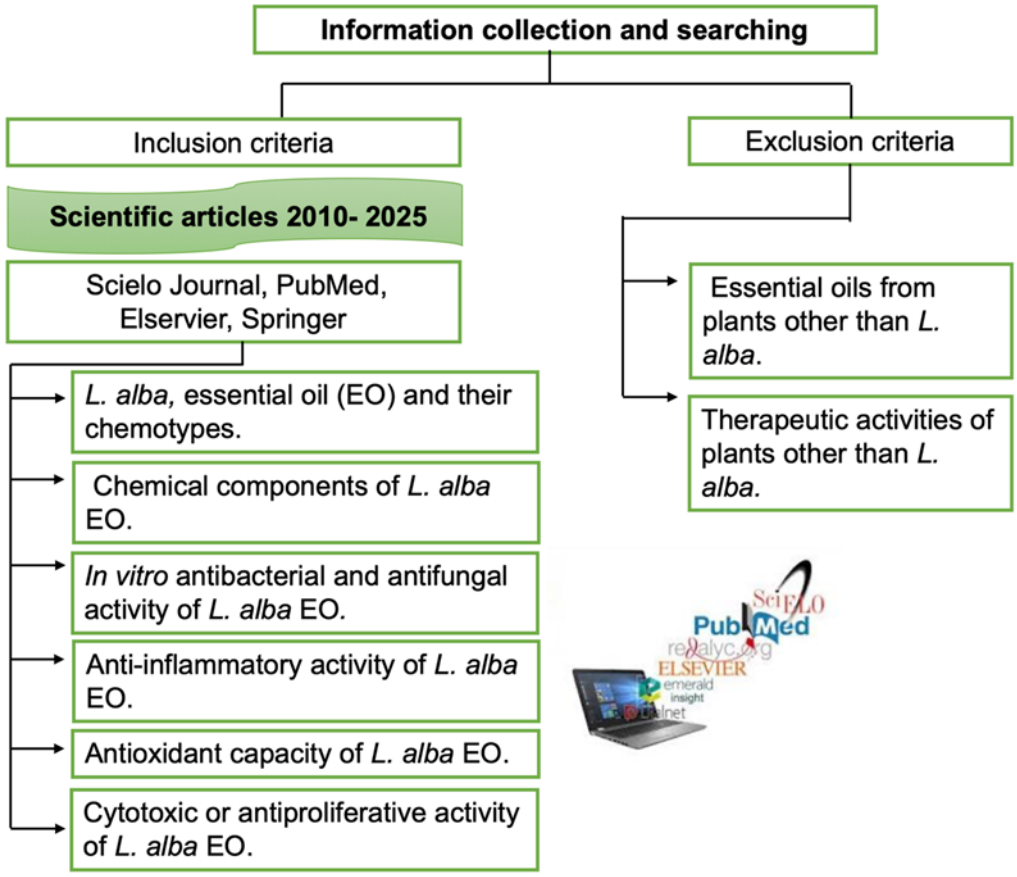

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Figure 1. Methodological diagram of the information search.

Results and discussion

L. alba has played a significant role in healthcare, and this review provides an overview of the plant's various chemotypes and their therapeutic properties. It begins by presenting evaluations of the essential oil's antibacterial and antifungal activity against pathogens that pose a threat to human health. Next, the antioxidant activity is discussed, with a focus on phenolic compounds, which exhibit a range of biological effects, including the scavenging of free radicals, an action that aids in reducing the incidence of several diseases associated with oxidative damage, such as Alzheimer's and Parkinson's diseases. Finally, the review offers a brief overview of the therapeutic potential of *L. alba*'s anti-inflammatory and antiviral activities, as well as its cytotoxic effects, highlighting its application in disease treatment.

L. alba chemotypes

The *L. alba* chemotypes are chemical variants of this aromatic plant, classified according to the main compound present in their essential oil (Louchard & Araujo, 2019). Numerous chemotypes of *L. alba* essential oil have been described, differentiated by the presence of dominant components (Fitzgerald *et al.*, 2015). Atti *et al.* (2002) were the first to report three chemotypes of *L. alba* with different pharmacological activities depending on their major constituents (citral-myrcene, citral, limonene, and carvone-limonene). Later, Tavares *et al.* (2005) identified three chemotypes with distinct compositions in various regions of Brazil (citral, carvone, and linalool). López *et al.* (2011) analyzed the composition of *L. alba* EOs and found six main components (citral, geraniol, trans-β-caryophyllene, carvone, limonene, and bicyclosesquiphellandrene). In Uruguay, Aular *et al.* (2019) reported two chemotypes: one containing camphor and 1,8-cineole, and the other with linalool as the main constituent. In Central America, the chemotype markers include limonene and piperitone in Guatemala; carvone in Cuba; and both limonene and carvone chemotypes in Costa Rica (Aular *et al.*, 2019).

Hennebelle *et al.* (2008) proposed a classification based on the comparative analysis of the chemical composition of EOs, identifying seven chemotypes: Chemotype I includes oils with citral, linalool, and β-caryophyllene as main components (with four subtypes); Chemotype II consists of oils in which tagetenone is the dominant compound; Chemotype III includes oils with high concentrations of limonene and a variable proportion of either carvone or other monoterpene ketones in place of carvone (with two subtypes); the remaining chemotypes are defined by a single predominant constituent, specifically: Chemotype IV with myrcene, V with γ-terpinene, VI with camphor and 1,8-cineole, and VII with estragole (Table 1).

Although several authors have proposed a unified classification for *L. alba* EO chemotypes,

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in practice, this is limited by the many factors that can influence the composition of the oil's constituents. This chemical variability presents a challenge for the product commercialization (Linde *et al.,* 2016).

Table 1. Classification of *L. alba* chemotypes.

Chemotype	Subtype	Majority component	Places where it has been described
I	Ia	Citral (a mixture of neral and geranial isomers) all year round.	Argentina, Brazil, Colombia, India, Martinique, and Guadeloupe Island.
	Ib	Linalool (all year round).	Argentina, Uruguay, Brazil, and India.
	Ic	Citral or Linalool (depending on the time of year).	Argentina.
	Id	β- caryophyllene.	Brazil.
II		Tagetene (mixture of myrcenone and ocimenone isomers).	Mexico, Guatemala, Costa Rica, and Argentina.
III	IIIa	Limonene and carvone.	Brazil, Colombia, Costa Rica, Cuba, Peru, French Guiana, and Martinique.
	IIIb	Limonene and any of the following cyclic ketones: dihydrocarvone, piperitone, piperitenone, lippione.	Argentina, Guatemala.
IV		Myrcene.	Argentina, India.
V		γ-Terpinene.	Brazil.
VI		Camphor and Eucalyptol.	Uruguay.
VII		Estragol (methyl chavicol).	USA, Mexico.

Prepared from: Atti *et al.* (2002), Tavares *et al.* (2005), Hennebelle *et al.* (2008) López *et al.* (2011), Aular *et al.* (2019).

Antibacterial activity

The global emergence of bacterial resistance to antibiotics has become a significant healthcare concern, necessitating the exploration of new alternatives to address this issue, particularly natural compounds, herbs, and phytochemicals (Prabu *et al.,* 2018). Herbal-based products may serve as effective and cost-efficient chemotherapeutic agents, providing a viable solution for controlling various pathogens (Harikrishnan *et al.,* 2011). EOs can inhibit bacterial growth through several mechanisms, including disrupting the outer membrane, increasing cell

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wall permeability, causing ion and cytoplasmic leakage, and ultimately inducing cell death. These effects are related to the lipophilic nature of EO components (Ara & Nur, 2009; Majolo *et al.,* 2017).

Juiz *et al.* (2015) demonstrated the antibacterial activity of *L. alba* EO extracted from leaves and flowers against periodontal pathogens (*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis,* and *Fusobacterium nucleatum*) *in vitro*; the minimum inhibitory concentration (MIC) for *P. gingivalis* using leaf-derived EO was 0.00625 mg/mL, while *A. actinomycetemcomitans* and *F. nucleatum* had MICs of >3.2 mg/mL and 0.8 mg/mL, respectively. For flower-derived EO, the lowest MIC was again for *P. gingivalis* (MIC, 0.0125 mg/mL), with higher MICs for *A. actinomycetemcomitans* and *F. nucleatum* (MIC, >3.2 and 0.8 mg/mL, respectively). Similarly, Majolo *et al.* (2016) reported the antibacterial activity of chemotype I (citral) *L. alba* EO against *Aeromonas hydrophila* via broth microdilution, showing inhibition at 5 mg/mL. Sutili *et al.* (2015) also noted bacteriostatic and bactericidal effects against *A. hydrophila* with MICs of 2.86 mg/mL and 5.99 mg/mL, respectively.

Santos *et al.* (2016) demonstrated the antagonistic effects of *L. alba* EO against pathogens such as *Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Enterococcus faecalis*, reporting an 80 % inhibition of *E. coli* growth. Other enteropathogenic bacteria (*S. marcescens, S. epidermis,* and *E. faecalis*) showed less than 70 % inhibition at a concentration of 4 mg/mL, while *P. aeruginosa* exhibited no response.

In Brazil, Mesquita *et al. (*2017) analyzed the *in vitro* antibacterial effect of *L. alba* essential oil and two of its components (citral and carvone) against *S. aureus*, using the microdilution assay in 96-well plates. They reported a MIC of 0.5 mg/mL for both the EO of *L. alba* and citral, while the MIC for carvone was 2.0 mg/mL. Metabolites such as citral are monoterpenes to which strong antibacterial activity is attributed, as they exert their effects by inducing changes in adenosine triphosphate (ATP) concentration, causing cell membrane hyperpolarization, and reducing cytoplasmic pH (Shi *et al.,* 2016). The results indicate a positive *in vitro* effect of the EOs against the growth of *S. aureus*, a clinically significant pathogen. Likewise, Islam *et al.* (2018) evaluated the *in vitro* antibacterial activity of *L. alba* leaf EO against six pathogens (*Sarcina lutea, Bacillus subtilis, E. coli, Pseudomonas sp., Klebsiella pneumoniae*, and *Xanthomonas campestris*). Antibacterial activity was qualitatively assessed based on the presence or absence of inhibition zones using the disk diffusion method. The EO exhibited antibacterial activity against two Gram-positive and four Gram-negative bacteria at a concentration of 15 mg/mL. The potential antibacterial effect of the EO may be attributed to the high oxygen content found in monoterpenes, primarily aldehydes and alcohols such as neral/geranial and nerol/geraniol (Oliveira *et al.*, 2006).

Couto *et al.* (2021) analyzed the antibacterial effect of the EO of *L. alba*, *Myrcia ludiana,* and *Ocimum basilicum* against six foodborne pathogens (*S. aureus, B. cereus, E. coli, Listeria monocytogenes, Salmonella typhimurium,* and *Enterobacter sakazakii*) using the disk diffusion method. They observed antibacterial activity with the treatment containing *L. alba* EO (MIC of 125 mg/mL) against all six pathogens evaluated. Similarly, Tubay-Bermúdez *et al.* (2024) conducted an antagonistic analysis of *L. alba* EO against *Photobacterium damselae* subsp. *Piscicida* and *B. subtilis* using the disk diffusion method, reporting inhibition zones of 56.7 mm and 9.7 mm,

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respectively. The main compounds in the EOs were neral (34.30 %) and geranial (45.57 %), which together constitute citral, a monoterpene already recognized for its antimicrobial activity. This compound disrupts the lipid structure of the bacterial cell wall, leading to protein denaturation and destruction of the cell membrane, which results in the loss of cytoplasmic contents and, ultimately, cell death (Weerawatanakorn *et al.,* 2015).

Antifungal activity

The reduction in the use of synthetic fungicides in agriculture is steadily increasing, while the use of natural products is seen as a promising alternative due to their lower negative environmental impact (Arango *et al.,* 2015). Fungi are a diverse group of eukaryotic microorganisms that have existed for over a billion years and constantly interact with humans. As a result of this interaction, a wide range of outcomes can occur, from the host eliminating fungi without pathology to severe infections that may lead to death (García & Carratalá, 2012). The EO of *L. alba* contains compounds that influence the growth of pathogenic fungi in humans, plants, and animals (Pérez *et al.,* 2017). This antifungal effect has been studied by several authors. For example, Glamoclija *et al.* (2011) evaluated the EO of *L. alba* against three *Aspergillus species* (*versicolor, niger,* and *fumigatus*), two *Penicillium* species (*ochrochloron* and *funiculosum*), and *Trichoderma viride*. They determined the MIC and minimum fungicidal concentration (MFC), reporting that the oil showed moderate to intermediate activity, with MIC values ranging from 0.300 to 1.250 mg/mL and MFC values between 0.600 to 1.250 mg/mL for all fungi tested, demonstrating that the EO is a viable option for controlling fungi that cause human disease. Ruiz *et al.* (2023) reported the antifungal effect of the carvone-limonene and citral chemotypes of *L. alba* EO at various concentrations (18.8, 28.1, 37.5, 53.6, and 75.0 mg/mL) against different *Candida strains*, with the highest antifungal activity observed in the carvone-limonene chemotype.

Compounds found in EOs, such as terpenoids, can integrate into fungal membranes, causing alterations in their structure and function. This disrupts essential processes such as protein synthesis and osmotic regulation. Additionally, some EO compounds can interfere with key metabolic pathways, such as ergosterol biosynthesis, a critical component of the fungal cell membrane (Singh *et al.*, 2015).

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Table 2. Antifungal activity of the main components of *L. alba* EO.

Fungi	Component	Inhibitory concentration	Reference
Candida parapsilosis, C. krusei, Aspergillus flavus, and A. fumigatus	Limonene	0.220, 0.140, 0.550, 3.5 mg/mL	Mesa-Arango *et al*. (2009)
A. ochraceus, Penicillium ochrochloron and *Trichoderma viride*	2,2,5-trimetil-3,4-hexanodiona, 3,5-dimetil-4-octanona y hexadecano.	0.300, 1.250, 1.250 mg/mL	Oliveira *et al.* (2014).
A. flavus	Geranial	0.28 mg/mL	Pandey *et al.* (2016)
Colletotrichum gloeosporioides	Citral	10.0 mg/mL	Pérez *et al.* (2017)
Mycobacterium tuberculosis	Geranial	1.250 mg/mL	Mota *et al.* (2018)
Fusarium pallidoroseum and *F. solani*	Citral	0.1 y 0.2 mg/mL	Peixoto *et al.* (2018)
A. niger	Linalool	0.300 mg/mL	Arruda *et al.* (2019)
Rhizoctonia solani	Linalool	0.5 mg/mL	Saroj *et al.* (2019)
Trichophyton rubrum and Candida spp.	Sabinene	2.5 y 5.0 mg/mL	Costa *et al.* (2020)
C. albicans, C. tropicalis and *C. parapsilosis*	Carvone	0.156, 1.250 and 5.0 mg/mL.	Sales *et al.* (2022)
A. flavus	Geranial/neral	1.0 mg/mL	Sabaly *et al.* (2024)

Carvone has demonstrated antifungal activity (Bouyahya *et al.*, 2021), with a mechanism of action involving structural destabilization of phospholipids, interaction with membrane proteins, and functioning as a proton exchanger, thereby disrupting the pH gradient across the membrane (Porfrio *et al.*, 2017). Limonene, another major component of *L. alba* EO, has been shown to induce oxidative stress in the cellular envelope, leading to DNA damage, modulation of the cell cycle,

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and induction of apoptosis via nucleolar stress (Irají *et al.*, 2020). In fact, limonene, a compound generally recognized as safe, has been reported to inhibit the growth of *Candida albicans* by inducing apoptosis through downregulation of Tps3 and activation of caspase (CaMca1) (Thakre *et al.*, 2018).

Antioxidant activity

In many biological systems, the overproduction of reactive oxygen species is a common consequence of stress, and this overproduction can be detected in tumors, chronic inflammation, and bacterial or viral infections (Jena *et al.*, 2023). Numerous studies have evaluated the antioxidant capacity of *L. alba* essential oil for many medical applications.

It has been confirmed that EOs from aromatic plants provide effects similar to current therapeutic approaches, as they exhibit multiple biological properties, including antioxidant activity due to their redox properties that neutralize free radicals, and anti-inflammatory activity by inhibiting histamine release and the activation of inflammatory mediators (Dhifi *et al.*, 2016).

The persistence of certain parasites and ongoing oxidative stress have been associated with diseases such as chronic Chagas disease. However, there are no efficient therapies for infections caused by *Trypanosoma cruzi.* Quintero *et al.* (2021) used EO fractions from two chemotypes of *L. alba* (citral and carvone), enriched with terpenes, to evaluate their effect on oxidative stress in macrophages infected with *T. cruzi.* They found that the carvone-limonene-enriched fraction reduced oxidative stress, selective antiproliferative action previously reported for limonene in cells sensitive to oxidative stress, such as tumor cells or protozoa, in which there is exacerbated proliferation accompanied by depletion of antioxidant defenses (Moreno *et al.*, 2018).

Given the importance of diseases associated with oxidative stress, the search for natural antioxidants is essential. Studies by Nonato *et al.* (2022) and Santos-Filho *et al.* (2023) investigated the antioxidant potential of *L. alba* EO, reporting significant antioxidant activity among the evaluated chemotypes, highlighting its potential for oxidative stress mitigation and food preservation.

Furthermore, Borromeo *et al.* (2024) evaluated the antioxidant properties of *L. alba* EO as a potential oxidative treatment in cancer cells. Their experiment was conducted on three aggressive breast cancer cell lines. Antioxidant activity was assessed through phenol and flavonoid quantification using the DPPH (2,2-diphenyl-1-picrylhydrazyl) method. EO treatment reduced cell proliferation, increased antioxidant activity and lipid peroxidation, and showed high cytotoxic effects associated with lactate dehydrogenase release. The findings offer a new perspective on the potential use of EO as a tool to counter proliferation in certain cancer cell lines.

Table 3 summarizes the antioxidant effects (IC_{50} = concentration that inhibits 50 % of free radicals) of various *L. alba* EO components.

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Table 3. Antioxidant activity of the components of *L. alba* EO.

Components of *L. alba* EO.	IC_{50} (mg/mL)	Free radical	Reference
Carvone, sesquiphelandrene bicycle, and limonene	10.88	TBARS	Olivero-Verbel *et al.* (2010)
Eucalyptol, myrcenone, and Z-ocimenone	12.45	DPPH	Reyes-Solano *et al.* (2017)
Linalool, eucalyptol, and sabinene	21.05	DPPH	Joshi *et al.* (2018)
Geranial/neral	0.0522	ABTS	Nonato *et al.* (2022)
Geranial, limonene, and neral	60.16	DPPH	Santos-Filho *et al.* (2023)
β-cis-terpineol	13.0	DPPH	Castro *et al*. (2023)
Citral	0.055	ABTS	Tubay-Bermúdez *et al*., (2024)

The antioxidant potential of *L. alba* and other *Lippia* species, such as *L. montevidensis* and *L. multiflora*, has been analyzed (Kapepula *et al*., 2017). Natural antioxidants can protect cells against ROS and, therefore, may help stabilize and protect tissues (Tumilaar *et al*., 2024).

Anti-inflammatory activity

Despite the traditional use of *L. alba* for pain and inflammatory disorders (Bonilla *et al*., 2022; Borges *et al*., 2022), relatively few studies have examined the pharmacological actions of its various chemotypes, such as the geraniol chemotype. One of the first reports of anti-inflammatory activity in *L. alba* was by Haldar *et al.* (2012), who evaluated leaf extracts in mice prepared by chloroform and ethanol extraction of powdered plant material. Their results revealed significant anti-inflammatory activity and identified key phytochemicals, including phytosterols, alkaloids, fixed oils, flavonoids, phenolic compounds, and saponins, among which flavonoids were deemed particularly important because they inhibit enzymes involved in inflammation, specifically blocking cellular mediators such as bradykinin and prostaglandins, thus, it was proposed that the plant could be effective against acute inflammatory disorders, providing a pharmacological rationale for its traditional use against painful or inflammatory conditions.

EO of *L. alba* chemotypes I and III has been reported to exhibit anti-inflammatory effects (Ortega *et al.,* 2020). This is supported by the study conducted by Sepúlveda *et al.* (2013), who

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analyzed the anti-inflammatory activity of the main constituents of various medicinal plants in Colombia. Carvone was identified as the major component in the EO extracted from *L. alba* (chemotype III). The anti-inflammatory effects were evaluated *in vitro* in murine macrophages stimulated with bacterial lipopolysaccharides. The obtained data showed that carvone exhibited the highest inhibitory effect on the production of inflammatory markers such as nitric oxide (NO), highlighting that epoxides from Colombian plants possess significant anti-inflammatory properties. Likewise, Swetha *et al.* (2018) conducted a study focusing on the anti-inflammatory activity of *L. alba* leaves in Wistar albino rats, using the carrageenan-induced paw edema model. In this experiment, four groups of animals were weighed and marked on their right hind limbs. The animals were divided into four groups, each consisting of 6 rats. The control group received a saline injection, the standard group was treated with ibuprofen, Test Group 1 (T1) received an ethanolic extract, and Test Group 2 (T2) received an aqueous extract of *L. alba* at a dose of 500 mg/kg. The anti-inflammatory effect was expressed as the percentage of edema inhibition. The mean paw thickness in the standard ibuprofen group was 4.7 ± 0.05, with an inhibition rate of approximately 66 % at 180 minutes. Group 1 showed a higher mean paw thickness of 5.12 ± 0.04, with an inhibition rate of around 40 % at 180 minutes, while Group 2 presented a value of 5.07 ± 0.06, with an inhibition rate of approximately 11 %. It was observed that the ethanolic extract at a dose of 500 mg/kg exhibited the highest anti-inflammatory activity among the tested extracts (compared to the aqueous extract) at 180 minutes. The results suggest that the main compound responsible for the anti-inflammatory effect may be present in the ethanolic extract. The anti-inflammatory activity of the ethanolic extract could be attributed to the presence of flavonoids.

Froz *et al.* (2024) demonstrated the anti-inflammatory effect of *L. alba* EO using the ear edema model, showing a reduction in edema that corresponded to an anti-inflammatory activity of 59.38 % at a dose of 25 mg/kg.

Antiviral activity

In recent decades, research aimed at evaluating the antiviral activity of bioactive compounds isolated from natural products has increased, offering an alternative path for the discovery of antiviral agents.

In studies conducted by Quispe *et al.* (2020), the antiviral activity of the *L. alba* EO was evaluated against the Zika virus (ZIKV); the oil was extracted using the hydrodistillation method and tested using a plaque reduction assay (PRA). The results showed that the EO exhibited antiviral effects at concentrations ranging from 8.02 µg/mL to 20.88 µg/mL, corresponding to plaque reduction percentages between 59.44 % and 85.56 %, suggesting its potential as a candidate for further studies against other viruses. Likewise, Silva *et al.* (2022) investigated the antiviral effects of EOs from Colombian plants against the dengue virus (DENV), both *in vitro* and *in silico*. A total of 14 different EOs were analyzed, including two chemotypes (citral and carvone) of *L. alba.* Cytopathic effect (CPE) reduction assays were performed, where CPE is defined as the biochemical and molecular damage caused by a viral agent. The CPE induced by DENV serves as a surrogate measure of viral replication *in vitro*, with lower CPE indicating greater antiviral activity. The results showed that *L. alba* EOs exhibited strong antiviral activity, with a half-maximal

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inhibitory concentration (IC_{50}) ranging from 29 µg/mL to 82 µg/mL, and reduced the CPE of both DENV serotypes by 32 % to 53 % at the highest concentration tested (100 µg/mL). Samples with higher contents of monoterpene alcohols or ketones, such as those from *L. alba* and *L. origanoides,* showed the strongest antiviral activity. This study is the first to report differences in the antiviral activity of EOs against DENV based on their monoterpene and sesquiterpene composition. These findings provide valuable information for the potential development of herbal-based prophylactic treatments for severe dengue. Sesquiterpene hydrocarbons and oxygenated monoterpenes may serve as starting materials for the development of antiviral phytopharmaceuticals (Silva *et al.*, 2024).

Evaluation of cytotoxicity, antiproliferative effect, and anticancer activity

Apoptosis, or programmed cell death, is a crucial mechanism for removing damaged or cancerous cells. Some studies suggest that *L. alba* extracts can induce apoptosis in various tumor cell lines through multiple molecular pathways. In particular, citral demonstrates a remarkable ability to activate apoptosis-related signaling pathways, such as caspase activation and the release of proteins from the mitochondrial intermembrane space, including cytochrome C (Singh *et al*., 2019). One major concern regarding the use of EOs is their potential cytotoxic effects; only a few studies have assessed this property to support their use as potential antimicrobial agents in humans, plants, and animals (Acero-Godoy *et al.,* 2019). Cytotoxic profiles at high concentrations have been reported, resulting in motor and hepatic neurological damage. For this reason, Aular *et al.* (2016) evaluated the chemical composition and toxicity of *L. alba* EO in mice. The results indicated a lethal dose of 2000 mg/kg body weight, with a 1500 mg/kg dose causing mortality in males but not in females, while 900 and 300 mg/kg doses showed no mortality. Furthermore, daily administration of 100 mg/kg for 28 days resulted in no toxicity or mortality, and no changes were noted in clinical parameters or the histopathology of analyzed organs. These findings suggest that *L. alba* EO can be safely used at appropriate doses as an antimicrobial or other beneficial compound.

Montero-Villegas *et al.* (2018) assessed the cytotoxic effects of EOs from four *L. alba* chemotypes (citral, limonene, caryophyllene, and geranial/neral) on human liver (HepG2) and lung (A549) cancer cell lines. MTT and apoptosis assays were employed to evaluate cytotoxicity and apoptosis induction. The results indicated that EOs from all four *L. alba* chemotypes exhibited significant cytotoxic effects in both cancer cell lines. However, the EO containing neral and geranial as major constituents displayed the highest cytotoxic activity. The effective concentration (IC_{50}) of the EOs ranged from 10 to 50 µg/mL. These findings suggest that L. alba EOs have potential as anticancer agents, with neral and geranial possibly responsible for these effects.

Acevedo-Estupiñan *et al.* (2019) demonstrated the effect of *L. alba* EO administration on obesity and T2DM markers in Wistar rats. Toxicity studies revealed that the tested doses (10, 200, and 500 mg/kg) were safe in both sexes, as no signs of toxicity or behavioral changes were observed. This was supported by liver function assessment, as hepatotoxicity markers AST and ALT showed no variation compared to the control group at the evaluated EO doses. Moreover,

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no deaths, behavioral changes, or hepatotoxicity were observed, whether with single or repeated EO doses. Thus, its LD_{50} is well above 500 mg/kg body weight. This is consistent with the findings of Olivero-Verbel *et al.* (2010), who evaluated the toxicity of *L. alba* Mill N.E. Brown EO, citral chemotype, administered intraperitoneally and found toxic effects only at doses equal to or greater than 1000 mg/kg (body weight) in mice.

Ortiz *et al.* (2021) analyzed EOs obtained from different *L. alba* chemotypes in the non-tumoral VERO cell line (kidney epithelium) and in tumor cell lines derived from brain, colon, lung, liver, stomach, breast, and skin cancers. Geraniol and *L. alba* EO showed significant cytotoxicity in gastric carcinoma cells, with IC_{50} values of 20 µM and 50 µg/mL, respectively. This effect was associated with the induction of apoptosis and inhibition of the PI3K/Akt signaling pathway, and it was selective for cancer cells, as no significant cytotoxicity was observed in non-cancerous cells.

The study conducted by Cavalcanti *et al.* (2023) aimed to evaluate the nephroprotective effect of the citral-limonene chemotype of *L. alba* EO due to its antioxidant properties in *in vivo* and *in vitro* models of acute kidney injury (AKI). One of the indicators of impaired renal function is the accumulation of nitrogenous metabolites, such as urea and creatinine. In this study, the ischemia/reperfusion (I/R) group presented elevated plasma levels of creatinine, uric acid, and urea, indicating renal damage. Pretreatment with *L. alba* EO partially prevented these changes, reducing nitrogen metabolites, preserving glomerular filtration rate via creatinine clearance, and partially preventing histological alterations.

Rodenak-Kladniew *et al.* (2023) investigated the cytotoxicity and anticancer activity of biocompatible lipid nanoparticles loaded with EOs from *L. alba* and *Clinopodium nepeta* against lung and colon cancer cells. Results showed that lipid nanoparticles loaded with EOs exhibited greater cytotoxicity against lung and colon cancer cells compared to untreated cells (IC_{50} range, 145–275 µL/L).

Although many EOs are generally recognized as safe, the use of herbs and EOs remains highly controversial, and their application in clinical practice is still restricted due to physicochemical properties (e.g., limited bioavailability) and/or toxicity (Seca & Pinto, 2018). However, they often serve as excellent leads for drug development; modifying and/or isolating their structures is a strategic way to enhance pharmacological action, as well as improve absorption, distribution, metabolism, and excretion properties, thereby reducing toxicity and side effects (Dosoky & Setzer, 2021).

Quintero *et al.* (2024) explored the adjuvant potential of *L. alba* EO fractions, citral chemotype, to enhance the efficacy and selectivity of two chemotherapeutic agents against acute myeloid leukemia (AML) cells. The analysis involved evaluating cytotoxic, genotoxic, oxidative stress, and cell death phenotypes induced by treatments in AML cells. According to the results, all EO-derived fractions exhibited significant antiproliferative activity against AML cells, but only one fraction demonstrated the highest antitumor and selective performance. This fraction was predominantly composed of citral (72 %), with a racemic mixture of neral (~40 %) and geranial (~32 %). Antiproliferative assays showed synergistic inhibitory effects on tumor cell growth

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with one of the agents and maintained low cytotoxicity in Vero cells. The observed selective antiproliferative effects may be attributed to the dual pro-oxidant/antioxidant behavior of citral in the citral chemotype *L. alba* EO.

Table 4 summarizes studies with different activities, along with the responsible components and their respective outcomes.

Table 4. Antiproliferative and anticancer activity of the main components of *L. alba* EO *in vivo*.

Component of *L. alba* EO.	Activity	Results	Reference
Geranial and citral	Antiproliferative effect on colon tumor cells.	The essential oils affected the cell line, inducing cell cycle arrests in the G0/G1 or G2/M phases. At doses of 50 and 100 µg/mL of *L. alba* oil, there was a significant increase in the G2/M phase; at concentrations of 10 µg/mL, an increase in cells in the G0/G1 phase was observed after 12 and 24 hours.	Gomide *et al.* (2016)
Citral	Antiproliferative activity in human leukemia cells.	Citral EOs produced under various conditions showed a cytotoxic effect on tumor cells ranging from 54 to 95 % (IS 1.8-8.6) and IC_{50} from 13 to 38.8 µg/mL.	Torcoroma-García *et al*. (2017)
Citral and limonene	Antispasmodic effect on tracheal smooth muscle contractions in rats.	Significant muscle relaxation effects were observed at concentrations ≥30 µg/mL for EO, ≥30 µg/mL for citral, and ≥600 µg/mL for limonene, in a concentration-dependent manner.	Carvalho *et al.* (2017)
Citral	Vasorelaxant effect on smooth muscle of rat aortas.	The components were able to cause significant relaxation in a concentration-dependent manner in aorta preparations with and without endothelium, at concentrations ≥ 10 µg/mL for AE and ≥ 30 µg/mL for citral.	Swetha *et al.* (2018)

Other research

L. alba is well known for its EOs, and several concentrations of compounds derived from different parts of the plant have been isolated and identified. Terpenes and their derivatives are the main constituents, generally known for their applications as flavors and fragrances. The structures of these compounds are variable, and their classification is based on the number of carbon chains and the chemical function presented. The main types of terpenes found in *L. alba* are monoterpenes and sesquiterpenes (Malik *et al.*, 2021).

Maynard *et al.* (2011) used *L. alba* EO, with citral as its major component, on rat mesenteric

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artery rings, showing an endothelium-independent vasorelaxant effect in both electromechanical coupling by potassium chloride (KCl 80 mM) and pharmacomechanical coupling by phenylephrine (1 µM), possibly due to inhibition of Ca^{2+} influx through L-type voltage-operated calcium channels (VOCCs).

The mechanism of muscle contraction can occur in two ways: depolarization of smooth muscle cells with potassium, which activates VOCCs and leads to increased intracellular calcium, this mechanism was mentioned above; and through pharmacological pathways, in which an external agonist binds to a membrane receptor coupled to a G protein, altering the activity of ion channels (Jackson & Boerman, 2018). Pereira-de-Morais *et al.* (2019) used *L. alba* EO, citral, or Limonene on rat uterus tissue, observing that the oil and each of its main terpene components produced a relaxing effect on contractions induced by various contractile agents. For both electromechanical and pharmacomechanical coupling via oxytocin, serotonin, and acetylcholine, all agents were equally effective in totally inhibiting contraction at the same concentration. However, when analyzing the inhibitory concentrations (IC_{50}) used, differences were found, with *L. alba* EO having lower IC_{50} values than citral and 1-limonene, suggesting that compounds present in lower concentrations in the EO may be active, possibly contributing to the relaxant effect.

Bonilla *et al.* (2022) reported an analysis of *L. alba* EO of the carvone chemotype on cell viability, lipid mobilization, and adipogenesis *in vitro*. The results showed that the EO did not reduce adipocyte viability at concentrations of 0.1, 1, and 5 µg/mL. Furthermore, changes were observed in lipid mobilization and adipogenesis, leading to a reversal of adipocyte hypertrophy. These results could be due to effects produced by the EO on lipogenic and lipolytic pathways, as well as modifications in the expression of adipogenesis-related genes. Thus, *L. alba* EO of the carvone chemotype could be considered a potential obesity treatment, using adipocytes as a therapeutic target.

Terpenes extracted from plants or their synthetic derivatives have become standard therapies for prostate, lung, ovarian, and breast cancers (Zhang *et al.*, 2018). Borges *et al.* (2022) studied the vasorelaxant effect of *L. alba* EO on the human umbilical artery, suggesting its potential use in treating hypertensive disorders during pregnancy. The study results indicate that *L. alba* EO reduced vascular tension in the human umbilical artery by 70.6 % at a concentration of 100 µg/mL. It was also shown to block voltage-operated calcium channels (VOCCs) by 60.2 % ± 4.5 % at the same concentration. These results may differ depending on the chemical composition of *L. alba* EO and the experimental conditions. Likewise, these conclusions are based on an *in vitro* study, and further research is needed to confirm these results in humans.

Conclusions

EOs from various aromatic plants, including *L. alba*, are gaining importance in many fields of biological research and have demonstrated therapeutic potential against different human pathogens. They exhibit antibacterial activity against *E. coli* and *S. aureus*, antifungal effects against *Aspergillus* spp., *T. viride*, and *Candida* spp., as well as antiviral activity against ZIKV and

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DENV in *in vitro* assays. Additionally, they possess anti-inflammatory, antioxidant, and antitumor properties. These findings may open new avenues for future research on *L. alba* essential oil in the biomedical field and plant biotechnology, focusing on *in vivo* studies using model organisms, thereby potentially providing a sustainable alternative to the excessive use of pharmaceuticals.

Author contributions

Work conceptualization: P.D.X.P., V.M.E.L.; Writing and preparation of the manuscript: H.L.S.R., P.D.X.P., and V.M.E.L.; Writing, review, and editing: H.L.S.R., C.T.J.A., N.P.E., G.M.L.C., M.A.I.G., P.D.X.P., and V.M.E.L.

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Conflicts of interest

The authors declare no conflicts of interest.

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