JOURNAL OF ESSENTIAL OIL RESEARCH
https://doi.org/10.1080/10412905.2021.1936667

Taylor & Francis
Taylor & Francis Group

REVIEW

New insights into the biotechnology and therapeutic potential of *Lippia alba* (Mill.) N.E.Br. ex P. Wilson

Sonia Malik[a,b], Samuel Odeyemi[c], Glaucia C. Pereira[d,e,f], Luciano Mamede de Freitas[a,g], Hazandy Abdul-Hamid[h,i], Narges Atabaki[j], Abdullah Makhzoum[k], Eduardo Bezerra de Almeida[b,g], John Dewar[c] and Rambod Abiri[h]

[a]Faculty of Science and Technology, Laboratoire De Biologie Des Ligneux Et Des Grandes Cultures (LBLGC), University of Orléans, Orleans, France; [b]Health Sciences Graduate Program, Biological & Health Sciences Centre, Federal University of Maranhão, Brazil; [c]Department of Life and Consumer Sciences, University of South Africa, Johannesburg, South Africa; [d]Biotechnology, Icelandic Institute for Intelligent Machines, Reykjavik, Iceland; [e]Department of Computer Sciences, Polytechnic Institute, University Autonoma of Madrid, Madrid, Spain; [f]Department of Bioengineering, Imperial College London, London, UK; [g]Laboratory of Botanical Studies, Department of Biology, Biological and Health Sciences Centre, Federal University of Maranhão, São Luís, Brazil; [h]Department of Forestry Science and Biodiversity, Faculty of Forestry and Environment, Universiti Putra Malaysia, Serdang, Malaysia; [i]Laboratory of Bioresource Management, Institute of Tropical Forestry and Forest Products (INTROP), Universiti Putra Malaysia, Serdang, Malaysia; [j]Department of Biochemistry, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, Serdang, Malaysia; [k]Department of Biological Sciences and Biotechnology, Botswana International University of Science and Technology, Palapye, Botswana

ABSTRACT

Lippia alba, commonly known as Bushy Matgrassis a well-known traditional herb. Besides being used as a food supplement, for seasoning and as a drink, this plant species possess several pharmacological properties, allowing its use in folk medicines to treat various diseases, especially those related to digestive and respiratory conditions. These properties are mainly attributed to the presence of compounds such as myrcene, linalool, β-ocimene, α-guaiene, germacrene, carvone, limonene, eucalyptol, camphor, caryophyllene, neral, geranial and piperitone in the essential oils of *L. alba*. Variation in essential oil components and the high phenotypical plasticity of *L. alba* provide a strong evidence of an exciting high number of chemotypes in this aromatic herb. In the current review, we report the botanical, geographical and ecological features of *L. alba*. In addition, chemical composition of essential oil is addressed followed by *in vitro* and high efficiency micropropagation protocols. Finally, the therapeutic potential of *L. alba* against important non-communicable diseases is discussed.

ARTICLE HISTORY
Received 28 September 2020
Accepted 25 May 2021

KEYWORDS
Lippia alba; pharmaceutical; essential oils; secondary compounds; immune system; *in vitro* culture; medicinal plant; plant natural products; verbenaceae

1. Introduction

The genus *Lippia* (Family Verbenaceae) contains nearly 200 species of trees, shrubs and herbs that are and widely disturbed in Central and South America as well as tropical Africa and Asia (1). This plant is traditionally used as a medicinal herb and applied an antiviral, antimalarial and cytostatic agent and as a respiratory and gastrointestinal remedy (2). Other pharmacological uses of this plant have in cardiovascular diseases, as an antioxidant and neurosedative, and for its anticonvulsiant activity and antiulcerogenic action. In addition, this herb is extensively applied as a food supplement and in infusions, drinks and seasoning (3). Morphologically, the genus *Lippia* has been categorized into seven different groups, out of which Zapania Schauer is the most famous and complex.It represents *L. rubella* (Moldenke) T.R.S. Silva & Salimena, *L. rotundifolia* Cham., *L. lacunosa* Mart. & Schauer, *L. hermannioides* Cham., *L. filifolia* Mart. & Schauer, *L. duartei* Moldenke, *L. diamantinensis* Glaz., *L. corymbosa* Cham., *L. brasiliensis* (Link) T.R.S. Silva, *L. aristata* Schauer and *L. alba* (Mill.) N.E.Br. in Brazilian flora (4,5).

Lippia alba (Mill.) N. E. Brown is an aromatic, tropical, vigorous and rustic shrub, which has been broadly cultivated in Brazil, Argentina, Colombia, Uruguay, Paraguay and Mexico (6). Common names for this plant vary in different regions and include Salvia Morada (Argentina), Melissa, Juanilama (Costa Rica), Oaxaca lemon verbana, Erva Cidreira (Brazil), Bushy Lippia, Bushy matgrass and Prontoalivio (Colombia). The compositional analysis of essential oils (EOs) of *L. alba* leaves indicates a variety of chemotypes according to major compounds such as carvone, citral and linalool in the oils (2,7). Additionally, other chemotypes such as myrcene, tagetone, citral/germacrened, limonene/carvone, β-caryophyllene and eucalyptol/limonene, camphor, eucalyptol were observed in their leaves (1,8). As with other species of *Lippia L. alba* has diverse pharmacological applications from its use as an

CONTACT Sonia Malik 777soniamalik@gmail.com

antipyretic, anti-inflammatory, acting as an antispasmodic and analgesic, to treating liver diseases and intestinal disorders (9).

Medicinal herbs like *L. alba* have played a significant role in health care and so the following review provides an overview on different aspects of this herb. Initially, botanical, geographical and ecological characteristics of this aromatic plant are broadly explained. Then, by focusing on the essential oil components, the chemical composition of *L. alba* is addressed. Micropropagation, regeneration and factors affecting the growth and yield of volatile compounds are reviewed to focus on optimal *in vitro* micropropagation conditions. Finally, a brief review of the therapeutic potential of this plant will be provided with a focus on treatment of non-communicable diseases such as cardiovascular disease and cancer. To appreciate fully the therapeutic potential of *L. alba*, this review will discuss several classes of compounds present in this plant species including terpenes, polyphenolics, saponins and iridoids.

2. Lippia alba

Lippia alba is a flowering plant species belonging to the family Verbenaceae, which includes about 175 genera and 2,800 species (10). The taxonomical features of this plant are shown in Table 1. The distribution of such plants includes the tropics and subtropics as well as temperate regions of the Southern Hemisphere (Table 2) (11). This plant family is important as it includes many medicinally important species, including the genera *Stachytarpheta, Lantana and Lippia* (12,13). The genus *Lippia* has 84 species, of which 60 are endemic to Brazil (14). This medicinal plant is used in folk medicine where it is popularly known as lemon grass, table-top tea, citron, wild rosemary, wild lemon, false melissa, Carmelite, Brazilian savior, sage, lemon lard, field rosemary and wild sage (15).

2.1 Morphology

Lippia alba is an ornamental plant that is developed as a sub-bush with a shrub that is about 1 to 1.5 m in height, with thin, arched, quadrangular, light brown to whitish branches (Figure 1). The petiole of this flowering plant is 0.5–1.3 cm long. Leaves are single, 1.3–3 cm long x 0.7–2 cm wide, with opposite filotaxia, presenting an oblong leaf blade that is elliptic to ovoid, elliptic-lanceolate, with an acute apex and cuneate base. The chartaceous leaves have a serrated margin, have a membranaceous consistency and a rough surface where the upper leaf face is glabrous while the lower face is tomentosa with glandular trichomes (16). It presents an axillary inflorescence, in glomerulus with short axis (7). Flowers are hermaphrodite, small chalice, ovoid, rosy-violet corolla with yellow nectar. It has four stamens, adhered petals, with yellow anthers of longitudinal opening. The ovary is superior, with two locules and an ovule. The fruit is globose, pear-shaped, bony with rosy-pink color seeds (17). In relation to anatomy, the plant has trichomes of the tectores type, unicellular and acicular. The lower and upper epidermis present cells in the form of a 'fit set' and undulating margins (18). (17).

Table 1. Taxonomic hierarchy of *L. alba* (120).

	Taxonomic Hierarchy
Kingdom	Plantae
Subkingdom	Vascular plants
Phylum	Tracheophyta
Division	Magnoliophyta
Class	Magnoliopsida
Clade	Angiosperms
Group	Eudicots
Subclass	Asterids
Order	Lamiales
Family	Verbenaceae
Genus	Lippia
Species	*Lippia alba*

Table 2. Worldwide distribution of *L. alba*. Source: http://www.plantsoftheworldonline.org.

Place	Disruption	Place	Disruption
Argentina Northeast	Native	El Salvador	Native
Argentina Northwest	Native	Florida	Native
Bahamas	Native	French Guiana	Native
Bolivia	Native	Guatmeala	Native
Brazil North	Native	Ecuador	Native
Brazil Northeast	Native	Haiti	Native
Brazil South	Native	Honduras	Native
Brazil Southeast	Native	Leeward Is	Native
Brazil West- Central	Native	Mexico Northeast	Native
Cayman Is	Native	Mexico Northwest	Native
Colombia	Native	Mexico Southwest	Native
Jamaica	Native	Panamá	Native
Mexico Central	Native	Peru	Native
Mexico Gulf	Native	Southwest Caribbean	Native
Mexico Southeast	Native	Texas	Native
Nicaragua	Native	Turks-Caicos Is.	Native
Paraguay	Native	Venezuela	Native
Puerto Rico	Native	Windward Is.	Native
Suriname	Native	Andaman Is.	Native
Trinidad-Tobago	Native	Assam	Introduced
Uruguay	Native	Bangladesh	Introduced
Venezuelan Antilles	Native	Central American Pac	Introduced
Costa Rica	Native	India	Introduced
Cuba	Native	Portugal	Introduced
Dominican Republic	Native	Queenslan	Introduced

2.2. Geographic Distribution

Lippia alba is widely distributed in America, ranging from the southern United States, Mexico and the West Indies to Argentina and Uruguay and is cultivated mainly for medicinal purposes (19). It grows in all the states of Brazil, most frequently on sandbanks in the Amazon region (17). It develops in Amazonian vegetation, Caatinga, Cerrado, Atlantic Forest, which is recorded in

Figure 1. General appearance of the species *Lippia alba* (Mill.) N.E.Br. ex P. Wilson, Verbenaceae family. 1A- general aspect of the plant; 1B- detail for inflorescence (Source: J. Medeiros).

the ciliary forest, Palmeiral, Restinga and in diverse environments from wet to dry areas and in sandy soils to anthropic areas (20,21). Figure 2 indicates the geographical distribution of *L. alba*.

Although *L. alba* is a native herb in some parts of the world like Brazil, Cuba, Costa Rica and Colombia, this plant has been introduced to some other parts such as India and Bangladesh (Table 2).

2.3 Ecological Adaptation

This wide geographical distribution of *L. alba* results in great phenotypic plasticity characterized mainly by the altered shape of the leaf (19). Studies indicate that the plant blooms throughout the year, with peak flowering in January, April, August and September. Fruiting is observed in January, August, October and December (17,22) and the reproductive phase might vary due to the environment in which plants are cultivated (23). The essential oils of the plant are aromatic and vary qualitatively and quantitatively due to factors such as flowering time, plant age, water quantity, geography, climatic factors and according to the seasons (7,24). These observations are useful when collecting plant material to optimize phytochemical yield and activity.

2.4. Chemical compounds of *Lippia alba*

Lippia. alba is well known for its essential oils (EOs) (25) particularly as varied concentrations of compounds have been isolated and identified from its EOs when derived from different parts of the plant (12). The compounds identified or isolated from *L. alba* have different medicinal purposes (26) including antioxidant, neurosedative, antimicrobial, antidiabetic, acaricidal and insect repellency activities (11,27–29). Classes of compounds as identified from *Lippia* (10) include terpenes,

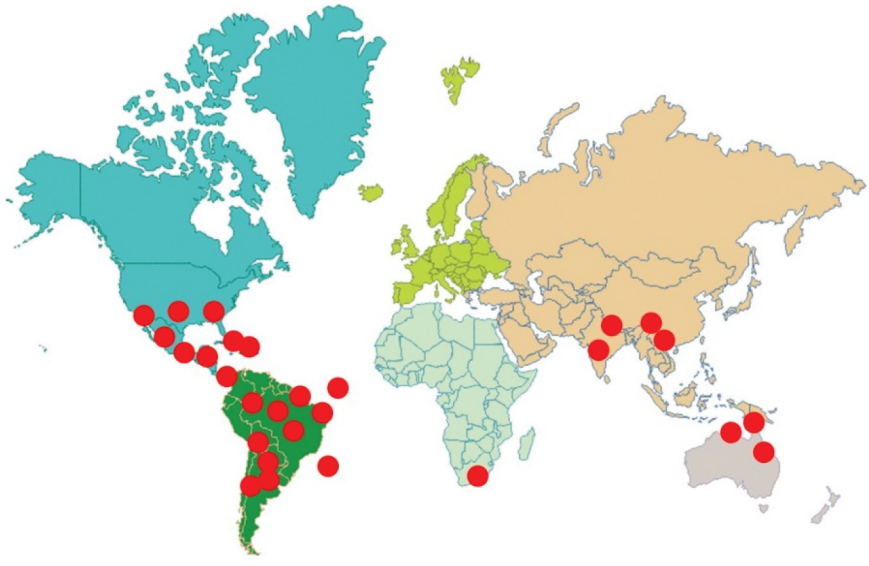

Figure 2. Schematic map of *Lippia alba* distribution across the world. Link: https://www.discoverlife.org/mp/20m?kind=Lippia+alba.

polyphenolics, saponins, iridoids and other compounds (29). The percentage yield of some of these compounds is summarized in Table 3.

2.4.1 Terpenes

Terpenes are the major constituents of the EOs from *L. alba* (34,35). These are generally known for their applications as flavors and fragrances (26). The structures of these terpenes are variable and are classified based on their number of carbon-chains (36) and the main types of terpenes found in *L. alba* are the monoterpenes and sesquiterpenes (37). The essential oils of *L. alba* contain more highly saturated terpenes than unsaturated terpenes but the latter are important as they coordinate metal complexes to their carbon–carbon double bonds (38). In *L. alba*, terpenes are produced by a group of enzymes called terpene synthases (TPS), which carries two conserved domains DDXXD/E and the 'NSE/DTE' motif (N/D)DXX(S/T)XXXE are the parts of magnesium binding during fixation of pyrophosphate substrate and a motif LQLYEASFLL t is involved in the active site of those enzymes. Genetic improvement and molecular biology of such enzymes and their genes are important keys to improve the quantity and quality of EOs in *L. alba*. The essential oils of *L. alba* contain more highly saturated terpenes than unsaturated terpenes but the latter are important as they coordinate metal complexes to their carbon–carbon double bonds (38).

Table 3. Common constituents in *Lippia alba* essential oils.

Constituents	Percentage yield	Ref.
Sabinene	0.05	32
Myrcene	0.2	30, 32
Limonene	2.5–7.32	30, 31, 32
Carvone	7.41	31, 32
Citral	59	31
Linalool	0.78–1.8	30,31,32
Piperitone	0.32	31,32
Neral	25.4–33.32	30,11
Geranial	33.1–50.94	30,11
Caryophyllene oxide	0.1–0.56- 2.17	30,31,11
Sesquiterpene hydrocarbons	13.6	30
Trans – caryophyllene	3.07–6.6	30,11
Cubebol	0.31	11
β-elemene	0.27–1.9	30,31,11
cis-α-bisabolene	0.12–0.6	30,31
Bicyclosesquiphellandrene	1.2	30
α-humulene	0.19–1.3	30,31,11
Rosefuran epoxide	0.1–0.19	30,11

2.4.2 Monoterpenes

Commonly identified monoterpenes detected in *L. alba* contain two or three double bonds (39) and may contain a terminal aldehyde moiety as in citral (Figure 3a) or monoterpene-ketones such as carvone (Figure 3b) (39). There are different citral isomers based on chemical constituents and neral and geranial are the main isomers of the citral chemotype (35). Carvone has a chiral center and can be biosynthesized in *L. alba* as either the R-(−)-carvone or the S-(+)-carvone enantiomer (40). Other monoterpenes include Myrcene (Figure 3c), an acyclic monoterpene that contains three double bonds, limonene (Figure 3d), a monocyclic monoterpene with two double bonds, as well as 1,8-cineole (Eucalyptol), and linalool (41).

2.4.3 Sesquiterpenes

The major sesquiterpenes detected in the EOs of *L. alba* are caryophyllene oxide, β-caryophyllene and E-caryophyllene (Figure 4a) (36). These compounds contribute to the unique aroma of its EOs and are known for their psychoactive effects (42,43) as well as antioxidant, antidepressant, anxiolytic, anti-inflammatory and anticancer properties (44). Other sesquiterpenes are cubebol (Figure 4b), elemene (Figure 4c), germacrene (Figure 4d) and humelene (Figure 4e). Cubebol possesses mosquito larvicidal activity and could be an effective antimalarial agent, while elemene, germacrene and humelene are effective antibacterial and anticancer agents (45).

2.4.4 Polyphenolics

The major polyphenolic compounds in *L. alba* are phenols and flavonoids (2). This group of compounds is

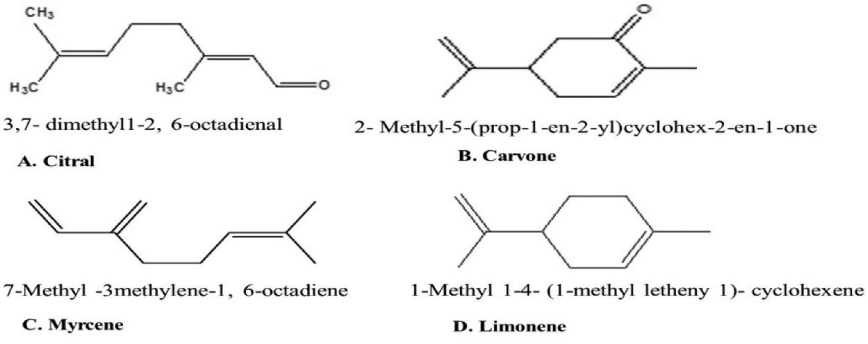

Figure 3. monoterpenes identified in *Lippia alba*.

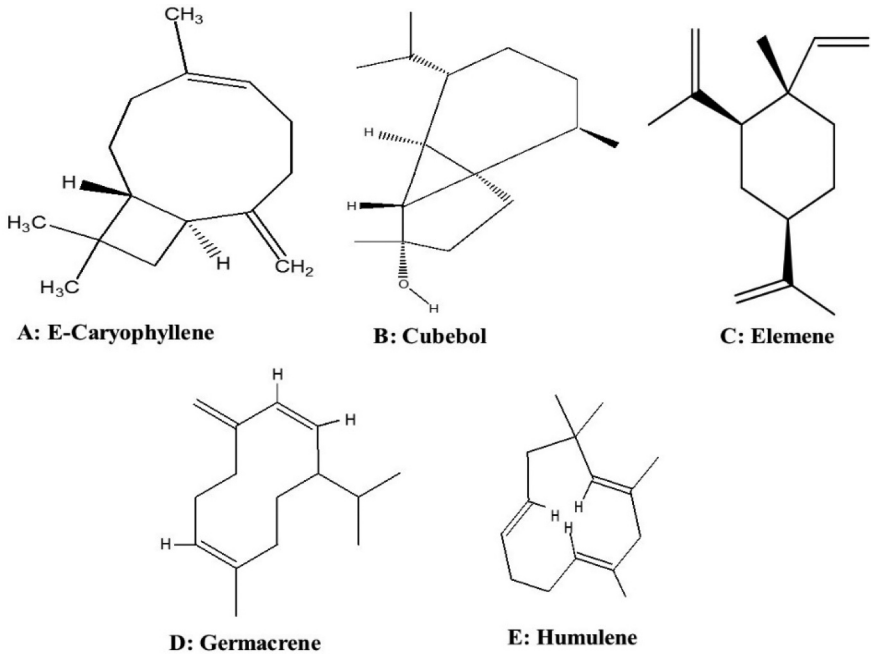

Figure 4. Sesquiterpenes identified in *Lippia alba*.

responsible for antioxidant, anesthetic, antibacterial and sedative activity following their interaction with central nervous system receptors such as BZD and $GABA_A$ (46). Some of these compounds are apigenin (Figure 5a), Calceolcrioside E (Figure 5b), ellagic acid (Figure 5c) and luteolin (Figure 5d). Other polyphenolic compounds include protocatechuic acid, isorhamnetin, salicylic acid, luteolin-7-diglucuronide and naringenin (47). Identified compounds also include phenylpropanoids (cistanoside F, forsythoside B, calceolarioside E, acteoside, isoacteoside and 2-acetylacteoside) and flavonoids (apigenin-7-O-glucuronide, luteolin-7-O-glucuronide, apigenin-7-O-diglucuronide and luteolin-7-O-diglueuronide) (42,48,49). Two bioflavonoids were identified in the aerial plant parts: 5,5”-dihydroxy-,4′,6”,3”’,4”’-pentamethoxy-[C7–O–C7”]-biflavone and 4′,4,5,5”-tetrahydroxy-6,6”,3”’-trimethoxy-[C7–O–C7”]- biflavone (50).

2.4.5 Iridoids

As indicated in Figure 6, iridoids are class of cyclopentane pyran monoterpenes that are characterized by a

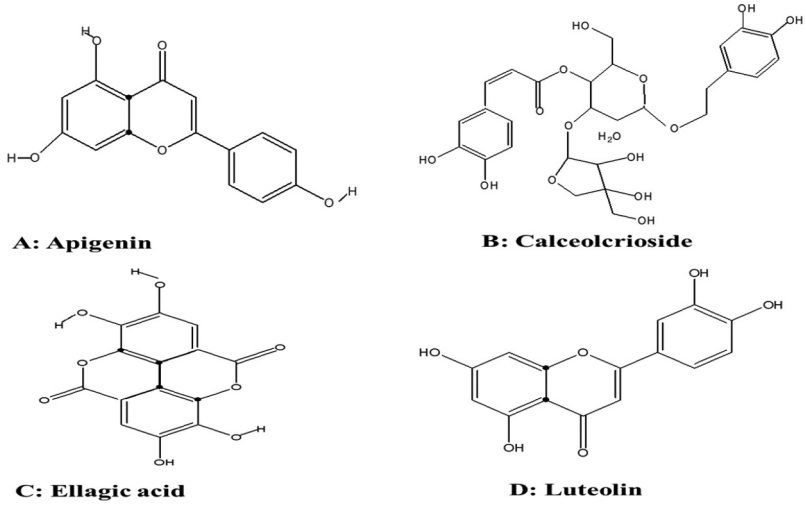

Figure 5. Polyphenolic compounds isolated from *L. alba*.

six-membered ring skeleton with an oxygen atom, fused to a cyclopentane ring (iridane skeleton) that are often linked to glucose and, hence, they are usually referred to as iridoid glycosides (2). This class of compounds is effective against a wide range of physical, chemical and biological stressors (49). The iridoids identified in the leaves and aerial parts of *L. alba* are theveside, geniposide or geniposidiic acid, 8-epiloganin, caryoptoside, shanzhiside methyl ester and mussaenoside (2,19). Although only the antioxidant and neurosedative properties of iridoids from *L. alba* have been reported, iridoids generally possess anticancer, antiaging, antibacterial, antiviral, antiallergic, cardio protective and hepatoprotective properties (2,19).

2.4.6 Saponins

As indicated in Figure 7, two saponins, Lippiasaponin I and Lippiasaponin II, have been isolated and identified from the leaves of *L. alba* using 96% ethanol (47). The hydrolysis of a mixture of these two compounds produced prosapogennin. Because of the squalene moieties in these saponins they are called triterpenoid saponins. The structure of Lippiasaponin I was elucidated as 3-O-β-D-glucopyranosyl-28-O-(α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl) n16α,23-dihydroxy-olean-12-en-28-oic acid while the structure of Lippiasaponin II was elucidated as 3-O-β-D-glucopyranosyl-28-O-(α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-α-Larabinopyranosyl)-16α,23-dihydroxy-olean-12-en-28-oic acid (51–53).

2.4.7 Other compounds identified from Lippia alba

Other compounds present in trace amounts in *L. alba* include cinerin, tannins, resins, mucilages, glycosides and steroid derivatives. As shown in Figure 8a, Cinerolone was identified from an oily ester named cinerin and is a compound with potent insecticidal activity. Also identified is a psychoactive isoxazole, Muscimol, that is known to be an agonist for all γ-aminobutyric acid type A receptor (GABAA-R) subtypes. Its structure is shown in Figure 8b. Other compounds present are isoelemicine and rose furan oxide which exhibit cytotoxic activity (Figure 8c and Figure 8d, respectively) (54–56).

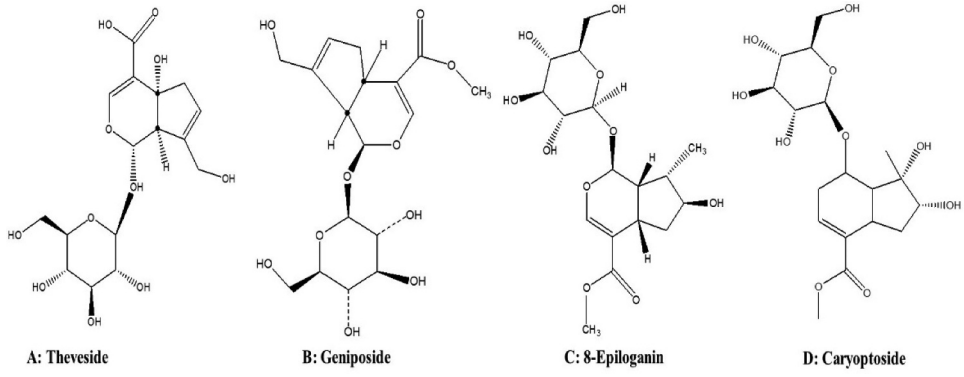

Figure 6. Iridoids isolated from *Lippia alba*.

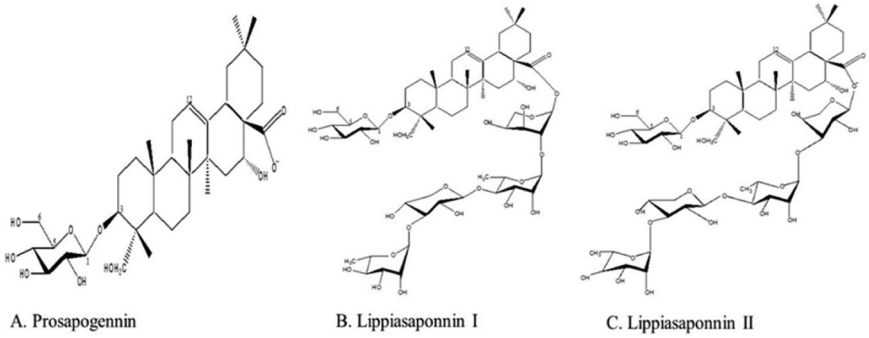

Figure 7. Saponins identified in *Lippia alba*. The hydrolysis of Lippiasaponnin I and II produces prosapogennin.

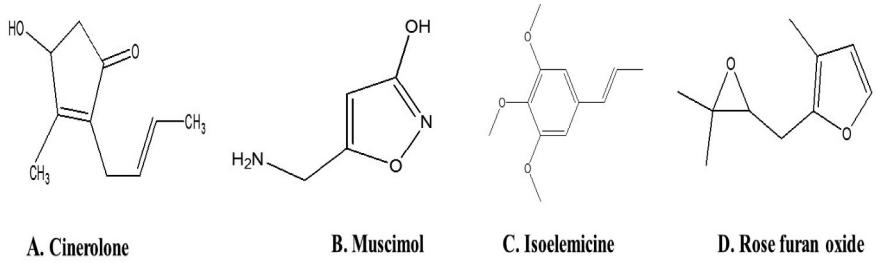

Figure 8. Various compounds identified in *Lippia alba*.

3. Micropropagation of *Lippia alba* and factors affecting yield of volatile compounds

Micropropagation is an important *in vitro* technique for rapid multiplication of selected plant species (57–61). This technique employs different basal media supplemented with varying concentrations of plant growth regulators in which apical and nodal plant segments are propagated to raise plantlets (62). Plantlets obtained through micropropagation are generally true to type. Publications have reported on *in vitro* culture of *L. alba* and subsequent isolation of essential oils (63,64). Multiple shoots derived from shoot tips of *L. alba* were obtained using Murashige and Skoog (MS) medium supplemented with 2 mg/mL 6-benzyl adenine (BAP). Rooted plantlets obtained in an MS medium devoid of plant growth regulators before being established in soil were found to possess identical essential oil profiles as well as morphology to that of vegetatively propagated plants (64).

Asmar et al. (65) studied the optimum concentration of BAP for *in vitro* multiplication of *L. alba* and found that using 1.5 mg/L BAP in the medium promoted *in vitro* multiplication – an increase in the shoot fresh and dry weights were obtained following the addition of BAP at 0.5 mg/L in the medium. However, the addition of growth regulators in the culture medium may effect essential oil production and quality by the plants (66). The oil yield was not shown to be significantly affected by varying the composition of the medium but quantitative variation was observed between the volatiles obtained from *in vitro* plantlets and mother plants. Thus, in comparison to the mother plants, plantlets cultivated in MS medium devoid of growth regulators produced lower amounts of α-pinene, (Z)-3-hexenyl acetate and α-gurjunene but more sabinene, myrcene, 1,8-cineole and p-mentha-1,5,8-triene. A significant increase in levels of sabinene and myrcene and decrease in linalool was reported in the presence of IAA (0.23 µM) in the culture medium as compared to MS medium without growth regulators. The addition of kinetin (0.92 µM) significantly increased the 3(S)-(+)-linalool level. It has been suggested that growth regulators influence the oil composition in *L. alba* by direct action on terpene metabolism independently of plant development efficiency and growth (66). Leaf and nodes have been reported to be the best explants for callus and shoot induction, respectively (48,66,67).

Light quality appears to significantly influence the *in vitro* growth and essential oil production in three chemotypes of *L. alba* (63,68). Thus, an increase in fresh and dry weight in chemotypes BEG-01 and BEG-02 was noted following their exposure to blue/red light-emitting diodes as compared to controls. Blue/red light-emitting diodes also induced higher photosynthetic pigment levels in all the chemotypes. In addition, the composition of volatile compounds (especially of eucalyptol and linalool) was reported to vary with light quality (63). Due to the relative ease in manipulating light quality, photoperiod and irradiance, *in vitro* culture is an important means to understand how metabolic pathways in different plant species are affected by electromagnetic radiation (69).

The environmental concentration of CO_2 was also reported to regulate the growth and quality of essential oil production in *L. alba* (68). Plant dry and fresh weight as well as total chlorophyll and carotenoid levels were found to be enhanced in BGEN-01 and BGEN-02 chemotypes upon enrichment with CO_2. The essential oil profile was also found to vary within and between different chemotypes. Thus, *Nerolidol/Linalool synthase* was reported to be upregulated only in the BGEN-01 chemotype following CO_2 treatment at 360 and 1000 µl/L (68). Those *L. alba* chemotypes with different ploidy levels including BGEN-01(triploid), BGEN-02 (diploid) and BGEN-42 (hexaploid) were evaluated for ethylene activity by culturing plants under *in vitro* conditions in the presence of the ethylene precursor (1-aminocyclopropane-1-carboxylic acid), the scavenger (mercury perchloride), the inhibitors (aminoethoxyvinylglycine and silver thiosulfate) and CO_2-enriched atmosphere (68). These conditions induced varied responses within

different chemotypes and ploidy levels with the most differentiated response pattern among the treatments being observed in hexaploidy chemotypes.

3.1. *In vitro* conservation

The advantages of *in vitro* conservation methods include reduction of labour costs, ease of exchange of plant material and optimum utilization of physical space (70–76). However, *in vitro* methods for germplasm conservation involve maintaining the plants under low temperature, reduced light intensity and varying media conditions and the use of such protocols results in slow growth (77). A protocol for *in vitro* conservation of five genotypes in *L. alba*; LA-13, LA-57 (carvone chemotype), LA-22 (linalool chemotype), LA-29 and LA-44 (citral chemotype) using mineral oil and reduced temperature (18°C and 23°C) was developed (78). However, mineral oil is a colourless and chemically inert liquid that provides the optimal environment for conservation and growth of explants, but plantlet growth is slow under the mineral oil because of the anaerobic environment (79). *In vitro* conservation of *L. alba* genotypes including the carvone chemotype was reported to be feasible for 270 and 180 days, respectively, following immersion in mineral oil and optimal at a temperature of 18°C. As expected, the carvone chemotype showed anatomical plasticity in response to different *in vitro* and *ex vitro* environments (78).

4. Therapeutic potential of *Lippia alba*

This section describes the clinical relevance of *L. alba* compounds particularly as they pertain to the treatment of two non-communicable diseases (NCD), cardiovascular conditions and malignant tumour.

The World Health Organization (WHO) reported that globally, cardiovascular disease (CVD) is among the major causes of mortality (80). To date, EOs derived from *L. alba* were used to treat medical conditions including hyperlipidemia and CVD and their mode of action is thought to suppress the synthesis of cholesterol and triacylglycerols to reduce intracellular concentration of lipids to induce an hypolipidemic response (81). The main limitation in investigating therapeutic use of *L. alba* chemotypes involves the efficient identification and modulation of biochemical targets in cell culture. Research has involved the use of liver-derived (HepG2) and non-liver (A549) human cell lines to monitor the regulation of lipogenic signaling cascades that are part of the mevalonic acid signalling chain (81). In this referenced study, the major research challenge was to identify multiple metabolic changes in target cells in response to the addition of specific essential oils using analysis of protein expression levels to identify hyperlipidemic biomarkers.

It has been suggested that at certain concentrations, *L. alba* EOs interfere with Ca^{2+} influx via the Ca^{2+} channel mechanism to induce endothelium-independent vasorelaxation. This has been equally observed after administration of other natural compounds well-known by their hypotensive effect (82–84). Such research showed that in rat mesenteric arteries, the essential oils of *L. alba* leaves, predominantly composed of geranial (48.58%) and neral (35.42%) modulate vasorelaxation in a manner similar to the action of drugs such as verapamil that are currently used to treat hypertension (83). A growing body of literature has detailed the mechanisms by which vasoconstriction and dilation occur. Researchers have attempted to draw fine distinctions between signalling cascades associated with the contraction of smooth muscles modulated by either Ca^{2+} influx or external increasing K^{+} concentration (85). Thus, removing or blocking Ca^{2+} channels results in suppression of smooth muscle contraction and such endothelium-independent Ca^{+2} channel arterial relaxation supports the hypothesis that signalling pathways inducing vasorelaxation are not necessarily modulated by endothelial cells (83).

The anti-hypotensive properties of medicinal plants have been reported in many papers (24,83,86–94) but care must be exercised as side effects regarding the use of extracts of *L. alba* to treat CVD have been identified (85). Nonetheless, significant progress into research on treating CVDs with medicinal extracts has been achieved. In addition to the effects of *L. alba* compounds on CVDs biomarkers, research has been published regarding the effects of ethanolic extracts of *L. alba* on vasocontraction-driven hypertension (87). These authors compared the relaxant effects of extracts of Colombian medicinal plants on contraction-induced aortic rings isolated from Spontaneously Hypertensive (SHR) and Wistar rats to show that the most pronounced concentration-dependent relaxant responses were associated with extracts from *Croton schiedeanus* and *Calea glomerata*, whereas extracts of *L. alba* contributed around a 40% reduction in the contraction induced by potassium chloride (KCl) of vascular smooth muscle and nearly 60% relaxation in phenylephrine-induced contraction. Research results involving modulation by medicinal extracts on voltage-dependent calcium channels and signal transduction pathways also confirmed published research results (83). As suggested by these authors, further investigation is needed to determine the effects of medicinal compounds on biomarkers and signalling cascade modulation and the possible development of adverse effects.

Research findings discussed in this section support the relevance of *L. alba* in CVD treatment, particularly based upon studies involving chemotype modulation of both hypertension and vasodilation (87), oxidative biomarkers (95) and inflammatory protein expression (96). However, it is essential to translate these research findings into clinical applications.

Research has pointed to the antioxidative potential of phenolic profiles within *L. alba* including flavonoids such as apigenin, luteolin, naringin and rutin, and their medical potential in mitigating tumour formation resulting from oxidative stress-driven gene mutations (95). Research results showed that the species exhibiting the highest naringin and total phenolic content, Santa Vitória do Palmar, was most effective in reducing hydrogen peroxide-induced oxidative damage in tissue homogenates of cerebellum, cerebral cortex, hippocampus and liver of Wistar rats. Such research results are important in drug repurposing because similar pathological trends related to oxidative impairment have been observed in brain cancer, particularly, mesenchymal glioblastoma. Thus, efficient therapy for treating grade IV glioma, based on *L. alba* phenolic profiles could revolutionise brain cancer therapy.

Partial reduction of oxygen yields reactive oxygen species (ROS) which are involved in maintenance of cellular stability. Likewise, overproduction of ROS, such as hydrogen peroxide-driven cell cycle impairment, may alter production of growth factor receptors, leading to cellular stress and disease progression, including treatment of brain cancer such as glioma (97). These research results further support the idea of challenging treatment design in both chemotherapy and radiotherapy, particularly complicated by drug-delivery challenges associated with the blood–brain barrier. These described treatment challenges underscore the importance of reviewing alternative treatment modalities such as those represented by extracts from plants such as *L. alba*, particularly as traditional phytomedicine has the advantages of easy access, low cost and, more recently, expansion to an increasing patient base via micropropagation (98).

Notwithstanding the relatively limited number of studies describing the potential of compounds from *L. alba* used to treat pathologies such as cardiovascular conditions and cancer, a growing body of literature offers valuable insights into impaired signalling cascades that can potentially be modulated via chemical compounds extracted from *L. alba*. Such compounds have the potential to mitigate oxidative stress-driven mutation and may inhibit immune dysfunction leading to chronic inflammatory affections. Together, the results of such research suggest that further investigation and experimentation into *L. alba* therapeutic properties is strongly recommended, because further studies can lead to novel drug discovery and medical treatment.

5 Conclusion

The demand for medicinal herbs has increased significantly as traditional herbs possess a variety of chemical components with diverse pharmacological activities. Thus far, several efficacious and potent medical treatments have been extracted from medicinal herbs and investigation of traditional herbs is vital to effectively contribute to medical therapy regimens, particularly against a background of the stresses of modern life. Studies of the therapeutic and biotechnological potential of EOs extracted from *L. alba* (Mill.) N.E.Br. ex P. Wilson have shown that this herb holds considerable promise as an alternative medication resource to treat a variety of diseases.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the author(s).

ORCID

Sonia Malik http://orcid.org/0000-0001-5224-3838
Samuel Odeyemi http://orcid.org/0000-0002-7580-6709
Rambod Abiri http://orcid.org/0000-0002-7538-1392

Reference

1. S. Nara, R.C. Pascon, M.A. Vallim, C.R. Figueiredo, M. G. Soares, J.H.G. Lago, et al. *Cytotoxic and antimicrobial constituents from the essential oil of Lippia alba (Verbenaceae)*. Medicines, **3**(3), 22 (2016). 10.3390/medicines3030022
2. T. Hennebelle, S. Sahpaz, B. Gressier, H. Joseph and F. Bailleul. *Antioxidant and neurosedative properties of polyphenols and iridoids from Lippia alba*. Phytotherapy Research: an International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, **22**(2), 256–258 (2008).
3. A.L.F. Gomes, M.P. Almeida, M.F. Leite, S. Schwaiger, H. Stuppner, M. Halabalaki, et al. *Seasonal variation in the chemical composition of two chemotypes of Lippia alba*. Food Chemistry, **273**, 186–193 (2019). 10.1016/j.foodchem.2017.11.089
4. R.W. Sanders. *The genera of Verbenaceae in the southeastern United States*. Harvard Papers in Botany, **5**, 303–358 (2001).
5. L. Viccini, P. Pierre, M. Praca, D.C.S.D. Da Costa, E. da Costa Romanel, S. De Sousa, et al. *Chromosome numbers in the genus Lippia (Verbenaceae)*. Plant Systematics and Evolution, **256**(1–4), 171–178 (2005). 10.1007/s00606-005-0351-3

6. T. Hennebelle, S. Sahpaz, H. Joseph and F. Bailleul. *Ethnopharmacology of Lippia alba*. Journal of Ethnopharmacology, **116**, 211–222 (2008). 10.1016/j.jep.2007.11.044
7. F.D.A. Matos. *As ervas cidreiras do Nordeste do Brasil. Estudo de tres quimiotipos de Lippia alba (Mill.) NE Brown (Verbenaceae) Parte II-Farmacoquimica*. Rev Bras Farm, **77**, 137–141 (1996).
8. M.D.G. Zoghbi, E.H. Andrade, A.S. Santos, M.H.L. Silva and J.G.S. Maia. *Essential oils of Lippia alba (Mill.) NE Br growing wild in the Brazilian Amazon*. Flavour and Fragrance Journal, **13**, 47–48 (1998).
9. M. Karl and J.A. Soderquist. *Alkylboranes in the Suzuki-Miyaura coupling: stereochemical and mechanistic studies*. The Journal of Organic Chemistry, **63**, 461–470 (1998).
10. A.F. Blank, L.C.A. Camelo, M.D.F. Arrigoni-Blank, J.B. Pinheiro, T.M. Andrade, E.D.S. Niculau, et al. *Chemical Diversity in Lippia alba (Mill.) N. E. Brown Germplasm*. The Scientific World Journal, **2015**, 1–11 (2015). 10.1155/2015/321924
11. J. Glamoclija, M. Sokovic, V. Tesevic, G.A. Linde and N. B. Colauto. *Chemical characterization of Lippia alba essential oil: an alternative to control green molds*. Brazilian Journal of Microbiology, **42**, 1537–1546 (2011). 10.1590/S1517-83822011000400041
12. C.M. Perez Zamora, C.A. Torres and M.B. Nunez. *Antimicrobial activity and chemical composition of essential oils from Verbenaceae species growing in South America*. Molecules, **23**, 544 (2018). 10.3390/molecules23030544
13. F. Salimena-Pires and A.M. Giulietti. *Flora Da Serra Do Cipo, Minas Gerais: Verbenaceae*. Universidade De São Paulo, **17**,155–186 (1998).
14. S. Daiane Rodrigues, *Insecticidal activity of extracts and essential oils of species of the genus Lippia against Callosobruchus maculatus (Fabricius, 1775) and Nasutitermes corniger (Motschulsky, 1855)* (2017).
15. H. Lorenzi and F. Matos. *Medicinal plants in Brazil: native and exotic*. Nov. Odes./Institu. Planta, **512**, 2002 (2002).
16. U.P. Albuquerque, U. Patil and A. Mathe. *Medicinal and Aromatic Plants of South America*. Springer, Netherlands (2018).
17. J.S.D. Santos, M.D.M.J. Iranildo, C.D. Abreu Maria and F. D.S. Margareth. *Verbenaceae sensu stricto in the region of Xingó: alagoas and Sergipe, Brazil*. Rodriguésia, **60**, 985–998 (2009). 10.1590/2175-7860200960412
18. J. Feix-Silva, I. Tomaz, M. Silva, K. Santos, A. Silva-Junior, M. Carvalho, et al. *Botanical and chemical identification of plant species of popular use in Rio Grande do Norte, Brazil*. Revista Brasileira De Plantas Medicinais, **14**(3), 548–555 (2012). 10.1590/S1516-05722012000300018
19. M. Pascual, K. Slowing, E. Carretero, D.S. Mata and A. Villar. *Lippia: traditional uses, chemistry and pharmacology: a review*. Journal of Ethnopharmacology, **76**, 201–214 (2001). 10.1016/S0378-8741(01)00234-3
20. S.M. Sousa, G.A. Torres and L.F. Viccini. *Karyological studies in Brazilian species of Lippia L. (Verbenaceae)*. Anais Da Academia Brasileira De Ciencias, **84**, 1029–1037 (2012). 10.1590/S0001-37652012005000068
21. S. Teles, J.A. Pereira, C.H. Santos, R.V. Menezes, R. Malheiro, A.M. Lucchese, et al. *Geographical origin and drying methodology may affect the essential oil of Lippia alba (Mill) NE Brown*. Industrial Crops and Products, **37**(1), 247–252 (2012). 10.1016/j.indcrop.2011.12.029
22. R. Montanari, L. Sousa, M. Leite, A. Coelho, L. Viccini and M. Stefanini. *Plasticidade fenotípica da morfologia externa de Lippia alba (Mill.) N. E. Br. ex Britt. & Wilson (Verbenaceae) em resposta a níveis de luminosidade e adubação*. Revista Brasileira De Plantas Medicinais, **6**(3), 96–101 (2004).
23. M.E. Duarte, P.E. Chetverikov, E.S. Silva and D. Navia. *Three new species of eriophyoid mites (Acariformes, Eriophyoidea) from Lippia alba (Verbenaceae) from Brazil, and remarks on the thorn-like spermathecal process*. Systematic and Applied Acarology, **21**, 1225–1249 (2016). 10.11158/saa.21.9.7
24. A. Meresa, N. Fekadu, S. Degu, A. Tadele and B. Geleta. *An ethno botanical review on medicinal plants used for the management of hypertension*. Clin Exp Pharmacol [Internet], **7**, 1–16 (2017).
25. P.J. Lima Juiz, A.M. Lucchese, R. Gambari, R. Piva, L. Penolazzi, M. Di Ciano, et al. *Essential oils and isolated compounds from Lippia alba leaves and flowers: antimicrobial activity and osteoclast apoptosis*. International Journal of Molecular Medicine, **35**(1), 211–217 (2014). 10.3892/ijmm.2014.1995
26. S. GarcIa-Abarrio, L. Martin, J. Burillo, G. Della Porta and A. Mainar. *Supercritical fluid extraction of volatile oil from Lippia alba (Mill.) cultivated in Aragon (Spain)*. The Journal of Supercritical Fluids, **94**, 206–211 (2014). 10.1016/j.supflu.2014.07.016
27. P.M. Carvalho, C.A. Macedo, T.F. Ribeiro, A.A. Silva, R.E. Da Silva, L.P. de Morais, et al. *Effect of the Lippia alba (Mill.) NE Brown essential oil and its main constituents, citral and limonene, on the tracheal smooth muscle of rats*. Biotechnology Reports, **17**, 31–34 (2018). 10.1016/j.btre.2017.12.002
28. K.O. Folashade and E.H. Omoregie. *Essential oil of Lippia multiflora Moldenke: a review*. Journal of Applied Pharmaceutical Science, **2**, 15–23 (2012).
29. G.A. Linde. *Chemotypes, extraction, chemical composition and use of Lippia alba essential oil*. Rev. Bras. Plantas Med, **18**(1), 191–200 (2016). 10.1590/1983-084X/15_037
30. M.A. López, E.E. Stashenko and J.L. Fuentes. *Chemical composition and antigenotoxic properties of Lippia alba essential oils*. Genetics and Molecular Biology, **34**, 479–488 (2011). 10.1590/S1415-47572011005000030
31. L.V.F. Flores da Silva, R.H.V. Mourão, J. Manimala and G. A. Lnenicka. *The essential oil of Lippia alba and its components affect Drosophila behavior and synaptic physiology*. Journal of Experimental Biology, **221**, jeb176909 (2018). 10.1242/jeb.176909

32 J. Glamočlija, M. Soković, V. Tešević, G.A. Linde, and N.B. Colauto. *Chemical characterization of Lippia alba essential oil: an alternative to control green molds*. Brazilian Journal of Microbiology, **42**, 1537–1546 (2011).

33. J.A. Pino, A. Ortega and A. Rosado. *Chemical Composition of the Essential Oil of Lippia alba (Mill.) N.E. Brown from*

Cuba. Journal of Essential Oil Research, **8**, 445–446 (1996). 10.1080/10412905.1996.9700662
34. Lim. *Quercus Infectoria Edible Medicinal and Non-Medicinal Plants,* pp. 16–26. Springer, Dordrecht (2012).
35. A.C. Mesa-Arango, J. Montiel-Ramos, B. Zapata, C. Durán, L. Betancur-Galvis and E. Stashenko. *Citral and carvone chemotypes from the essential oils of Colombian Lippia alba (Mill.) N.E. Brown: composition, cytotoxicity and antifungal activity*. Memórias Do Instituto Oswaldo Cruz, **104**, 878–884 (2009). 10.1590/S0074-02762009000600010
36. C.A. Catalan and M.E. De Lampasona. *The chemistry of the genus Lippia (Verbenaceae)*. Oregano: The Genera Origanum and Lippia, **1**, 127–149 (2002).
37. F. Terblanche and G. Kornelius. *Essential Oil Constituents of the Genus Lippia (Verbenaceae)—A Literature Review*. Journal of Essential Oil Research, **8**, 471–485 (1996). 10.1080/10412905.1996.9700673
38. M.R. Soto-Vasquez and P.A.A. Alvarado-Garcia. *Anxiolytic-like effect of Lippia alba essential oil: a randomized, placebo-controlled trial*. Journal of Complemtary Medicine Research, **7**, 101–107 (2018).
39. H.F. Linskens and J.F. Jackson. *Essential Oils and Waxes*. Springer-Verlag, Berlin, Heidelberg (1991).
40. R. Chizzola. *Regular monoterpenes and sesquiterpenes (essential oils)*. Natural Products, **10**, 978 (2013).
41. E. Van de Vel, I. Sampers and K. Raes. *A review on influencing factors on the minimum inhibitory concentration of essential oils*. Critical Reviews in Food Science and Nutrition, **59**, 357–378 (2019). 10.1080/10408398.2017.1371112
42. H. Tsuchiya. *Anesthetic agents of plant origin: a review of phytochemicals with anesthetic activity*. Molecules, **22**, 1369 (2017). 10.3390/molecules22081369
43. P. Villalobos and I.I. Wistuba. *Lung cancer biomarkers*. Hematology/Oncology Clinics of North America, **31**, 13–29 (2017). 10.1016/j.hoc.2016.08.006
44. M. Parente, F.R. Custodio, N.A.J. Cardoso, M.R.J.A. Lima, T.S.D. Melo, M.I. Linhares, et al. *Antidepressant-like effect of Lippia sidoides CHAM (verbenaceae) essential oil and its major compound thymol in mice*. Scientia Pharmaceutica, **86**(3), 27 (2018). 10.3390/scipharm86030027
45. G.N. Pandiyan, N. Mathew and S. Munusamy. *Larvicidal activity of selected essential oil in synergized combinations against Aedes aegypti*. Ecotoxicology and Environmental Safety, **174**, 549–556 (2019). 10.1016/j.ecoenv.2019.03.019
46. S. Odeyemi and J. Dewar. *Repression of Acetaminophen-Induced Hepatotoxicity in HepG2 Cells by Polyphenolic Compounds from Lauridia tetragona (L.f.) R.H. Archer*. Molecules, **24**, 2118 (2019). 10.3390/molecules24112118
47. F. Barbosa, M. Lima, R. Braz-Filho and E. Silveira. *Iridoid and phenylethanoid glycosides from Lippia alba*. Biochemical Systematics and Ecology, **34**, 819–821 (2006). 10.1016/j.bse.2006.06.006
48. D.O. Souza, V.D.S. Sales, C.K. de Souza Rodrigues, L.R. de Oliveira, I.C.S. Lemos, G. de Araujo Delmondes, et al. *Phytochemical analysis and central effects of Annona muricata Linnaeus: possible involvement of the gabaergic and monoaminergic systems*. Iranian Journal of Pharmaceutical Research: IJPR, **17**(4), 1306 (2018).
49. T. Hennebelle, S. Sahpaz, H. Joseph and F. Bailleul. *Phenolics and Iridoids of Lippia alba*. Natural Product Communications, **1**, 1934578X0600100906 (2006). 10.1177/1934578X0600100906
50. F. Barbosa, M.A.S. Lima and E.R. Silveira. *Total NMR assignments of new [C7?O?C7?]-biflavones from leaves of the limonene-carvone chemotype ofLippia alba (Mill) N. E. Brown*. Magnetic Resonance in Chemistry, **43**, 334–338 (2005). 10.1002/mrc.1546
51. J.-Y. Liu, Y.-L. Guan, L.-B. Zou, Y.-X. Gong, H.-M. Hua, Y.-N. Xu, et al. *Saponins with neuroprotective effects from the roots of Pulsatilla cernua*. Molecules, **17**(5), 5520–5531 (2012). 10.3390/molecules17055520
52. R. Upadhyay, M. Pandey, R. Jha and V. Pandey. *Eclalbatin, a Triterpene Saponin from Eclipta alba*. Journal of Asian Natural Products Research, **3**, 213–217 (2001). 10.1080/10286020108041393
53. Y. Xu, L. Bai, Y. Liu, Y. Liu, T. Xu, et al. *A new triterpenoid saponin from Pulsatilla cernua*. Molecules, **15**(3), 1891–1897 (2010). 10.3390/molecules15031891
54. M.E.M. Braga, P.A.D. Ehlert, L.C. Ming and M.A.A. Meireles. *Supercritical fluid extraction from Lippia alba: global yields, kinetic data, and extract chemical composition*. The Journal of Supercritical Fluids, **34**, 149–156 (2005). 10.1016/j.supflu.2004.11.008
55. M.A. da Cunha, F.M.C. de Barros, L. de Oliveira Garcia, A.P. de Lima Veeck, B.M. Heinzmann, V.L. Loro, et al. *Essential oil of Lippia alba: a new anesthetic for silver catfish, Rhamdia quelen*. Aquaculture, **306**(1–4), 403–406 (2010). 10.1016/j.aquaculture.2010.06.014
56. M. Zetola, T. De Lima, D. Sonaglio, G. González-Ortega, R. Limberger, P. Petrovick, et al. *CNS activities of liquid and spray-dried extracts from Lippia alba—Verbenaceae (Brazilian false melissa)*. Journal of Ethnopharmacology, **82**(2–3), 207–215 (2002). 10.1016/S0378-8741(02)00187-3
57. S. Malik, M. Sharma and P.S. Ahuja. *An efficient and economic method for in vitro propagation of Arnebia euchroma using liquid culture system*. American Journal of Biotechnology and Medical Research, **1**, 19–25 (2016). 10.5455/ajbmr.20160501100040
58. S. Malik, R. Kumar, S.K. Vats, S. Bhushan, M. Sharma and P.S. Ahuja. *Regeneration in Rheum emodi Wall . : a step towards conservation of an endangered medicinal plant species*. Engineering in Life Sciences, **9**(2), 130–134 (2009). 10.1002/elsc.200800071
59. S. Malik, N. Sharma, U.K. Sharma, N.P. Singh, S. Bhushan, M. Sharma, A.K. Sinha and P.S. Ahuja. *Qualitative and quantitative analysis of anthraquinone derivatives in rhizomes of tissue culture-raised Rheum emodi Wall. plants*. Journal of Plant Physiology, **167**(9), 749–756 (2010a). 10.1016/j.jplph.2009.12.007
60. S. Malik, S. Sharma, M. Sharma and P.S. Ahuja. *Direct shoot regeneration from intact leaves of Arnebia euchroma (Royle) Johnston using thidiazuron*. Cell Biology International, **34**, 537–542 (2010b). 10.1042/CBI20090372
61. M. Maluszynski, B.S. Ahloowalia and B. Sigurbjornsson. *Application of in vivo and in vitro*

mutation techniques for crop improvement. Euphytica, **85**, 303–315 (1995). 10.1007/BF00023960
62. S.E. Rozali, K.A. Rashid and R.M. Taha. *Micropropagation of an exotic ornamental plant, Calathea crotalifera, for production of high quality plantlets*. The Scientific World Journal, **2014**, Article ID 457092, 12pp (2014).
63. D.S. Batista, K.M. de Castro, A.R. da Silva, M.L. Teixeira, T.A. Sales, L.I. Soares, et al. *Light quality affects in vitro growth and essential oil profile in Lippia alba (Verbenaceae)*. In Vitro Cellular & Developmental Biology-Plant, **52**(3), 276–282 (2016). 10.1007/s11627-016-9761-x
64. S.K. Gupta, S. Khanuja and S. Kumar. *In vitro micropropagation of Lippia alba*. Current Science-Banglore, **81**, 206–209 (2001).
65. S.A. Asmar, R.F. Resende, E.C. Araruna, T.P. Morais and J.M.Q. Luz. *Concentrações de BAP sobre a proliferação in vitro de brotos de Lippia alba [(Mill.)N.E.Brown]*. Revista Brasileira De Plantas Medicinais, **14**(spe), 149–153 (2012). 10.1590/S1516-05722012000500004
66. E.S. Tavares, D. Lopes, H.R. Bizzo, C.L.S. Lage and S.G. Leitao. *Kinetin Enhanced Linalool Production by in vitro Plantlets of Lippia alba*. Journal of Essential Oil Research, **16**, 405–408 (2004). 10.1080/10412905.2004.9698756
67. M. Tafani, M. Di Vito, A. Frati, L. Pellegrini, E. De Santis, G. Sette, et al. *Pro-inflammatory gene expression in solid glioblastoma microenvironment and in hypoxic stem cells from human glioblastoma*. Journal of Neuroinflammation, **8**(1), 1–16 (2011). 10.1186/1742-2094-8-32
68. T. Baptista, S. Grunberg, N. Minoungou, M.J.E. Koster, H.T.M. Timmers, S. Hahn, et al. *SAGA is a general cofactor for RNA polymerase II transcription*. Molecular Cell, **68**(1), 130–143 (2017). 10.1016/j.molcel.2017.08.016
69. A. Saez-Cirion, C. Bacchus, L. Hocqueloux, V. Avettand-Fenoel, I. Girault, C. Lecuroux, et al. *Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study*. PLoS Pathogens, **9**(3), e1003211 (2013). 10.1371/journal.ppat.1003211
70. F. Engelmann, *In vitro* conservation methods. Biotechnology in Agriculture Series, 119–162 (1997).
71. F. Engelmann. *Use of biotechnologies for the conservation of plant biodiversity*. In Vitro Cellular & Developmental Biology - Plant, **17**, 5–16 (2012). 10.1007/s11627-010-9327-2
72. A. Gallego, S. Malik, M. Yousefzadi, A. Makhzoum, J. Tremouillaux-Guiller and M. Bonfill. *Taxol from Corylus avellana: paving the way for a new source of this anti-cancer drug*. Plant Cell Tissue and Organ Culture, **29**, 1–16 (2017).
73. S. Malik, O. Biba, J. Gruz, R.R.J. Arroo and M. Strnad. *Biotechnological approaches for producing aryltetralin lignans from Linum species*. Phytochemistry Reviews, **13**, 893–913 (2014).
74. S. Malik, S. Bhushan, M. Sharma and P.S. Ahuja. *Biotechnological approaches to the production of shikonins: a critical review with recent updates*. Critical Reviews in Biotechnology, **16**, 1–14 (2014b).
75. S. Malik, M.H. Mirjalili, A.G. Fett-Neto, P. Mazzafera and M. Bonfill. *Living between two worlds: two-phase culture systems for producing plant secondary metabolites*. Critical Reviews in Biotechnology, **33**, 1–22 (2013).
76. S. Malik, R.M. Cusidó, M.H. Mirjalili, E. Moyano, J. Palazón and M. Bonfill. *Production of the anticancer drug taxol in Taxus baccata suspension cultures: a review*. Process Biochemistry, **46**, 23–34 (2011).
77. S. Chanda and R. Dave. *In vitro models for antioxidant activity evaluation and some medicinal plants possessing antioxidant properties: an overview*. African Journal of Microbiology Research, **3**, 981–996 (2009).
78. M.G. Peixoto, A.C.L.D.O. Machado, A.F. Blank, J.H.S. Silva, J.M.Q. Luz and M.D.F. Arrigoni-Blank. *In vitro conservation and leaf anatomy of different chemotypes of Lippia alba (Mill.) NE Br*. Bioscience Journal, **33**(1), 41–51 (2017).
79. J. Mathur, S. Mukunthakumar, S. Gupta and S. Mathur. *Growth and morphogenesis of plant tissue cultures under mineral-oil*. Plant Science, **74**, 249–254 (1991).
80. N.U.A. Manaf, A. Ahmad and N.A.M.A. Yusoff. *Systematic Review on Long Term Effects of Weight Loss Diet on Body Weight and Lipid Profile: findings from Randomized Controlled Trials*. Universal Journal of Public Health, **6**, 40–48 (2018).
81. R.B. Singh, S.A. Mengi, Y.-J. Xu, A.S. Arneja and N.S. Dhalla. *Pathogenesis of atherosclerosis: a multifactorial process*. Experimental and Clinical Cardiology Springer, **7**, 40–53 (2002).
82. I.A.C. De Menezes, I.J.A. Moreira, J.W.A. De Paula, A. F. Blank, A.R. Antoniolli, L.J. Quintans Junior, et al. *Cardiovascular effects induced by Cymbopogon winterianus essential oil in rats: involvement of calcium channels and vagal pathway*. Journal of Pharmacy and Pharmacology, **62**(2), 215–221 (2010).
83. L.G. Maynard, K.C. Santos, P.S. Cunha, A.S. Barreto, M.G. Peixoto, F. Arrigoni-Blank, et al. *Chemical composition and vasorelaxant effect induced by the essential oil of Lippia alba (Mill.) NE Brown. (Verbenaceae) in rat mesenteric artery*. Indian Journal of Pharmacology, **43**(6), 694 (2011).
84. Y. Shiina, N. Funabashi, K. Lee, T. Toyoda, T. Sekine, S. Honjo, et al. *Relaxation effects of lavender aromatherapy improve coronary flow velocity reserve in healthy men evaluated by transthoracic Doppler echocardiography*. International Journal of Cardiology, **129**(2), 193–197 (2008).
85. B. Baharvand-Ahmadi, M. Bahmani, P. Tajeddini, M. Rafieian-Kopaei and N. Naghdi. *An ethnobotanical study of medicinal plants administered for the treatment of hypertension*. Journal of Renal Injury Prevention, **5**, 123 (2016).
86. M. Guerrero, P. Puebla, R. Carron, M. Martin, L. Arteaga and L. San Roman. *Assessment of the antihypertensive and vasodilator effects of ethanolic extracts of some Colombian medicinal plants*. Journal of Ethnopharmacology, **80**, 37–42 (2002).
87. E. Kakudidi, C. Kirimuhuzya, G. Anywar, E. Katuura and J. Kiguli. *Medicinal plants used in the management of noncommunicable diseases in Uganda*. In: *Medicinal Plants-Recent Advances in Research and Development*. Edits., H.S. Tsay, L.F. Shyur, D. Agrawal, Y.C. Wu and

S.Y. Wang, pp. 397–418, Springer, Singapore (2016). https://doi.org/10.1007/978-981-10-1085-9_17
88. N. Rajurkar and M. Damame. *Elemental analysis of some herbal plants used in the treatment of cardiovascular diseases by NAA and AAS*. Journal of Radioanalytical and Nuclear Chemistry, **219**, 77–80 (1997).
89. P. Rawat, P.K. Singh and V. Kumar. *Anti-hypertensive medicinal plants and their mode of action*. Journal of Herbal Medicine, **6**, 107–118 (2016).
90. H. Rouhi-Boroujeni, E. Heidarian, H. Rouhi-Boroujeni, F. Deris and M. Rafieian-Kopaei. *Medicinal plants with multiple effects on cardiovascular diseases: a systematic review*. Current Pharmaceutical Design, **23**, 999–1015 (2017).
91. S.M. Seck, D. Doupa, D.G. Dia, E.A. Diop, D.L. Ardiet, R.C. Nogueira, et al. *Clinical efficacy of African traditional medicines in hypertension: a randomized controlled trial with Combretum micranthum and Hibiscus sabdariffa*. Journal of Human Hypertension, **32**(1), 75–81 (2018).
92. Z. Sobhani, S. Reza Nami, S. Ahmad Emami, A. Sahebkar and B. Javadi. *Medicinal plants targeting cardiovascular diseases in view of Avicenna*. Current Pharmaceutical Design, **23**, 2428–2443 (2017).
93. N. Tabassum and F. Ahmad. *Role of natural herbs in the treatment of hypertension*. Pharmacognosy Reviews, **5**, 30 (2011).
94. S. Suroowan and F. Mahomoodally. *Common phytoremedies used against cardiovascular diseases and their potential to induce adverse events in cardiovascular patients*. Clinical Phytoscience, **1**(1), 1–13 (2015).
95. C.E. Chies, C.S. Branco, G. Scola, F. Agostini, A.E. Gower and M. Salvador. *Antioxidant Effect of Lippia alba (Miller) NE Brown*. Antioxidants, **2**, 194–205 (2013).
96. G.S. Viana, T.G.D. Vale, V. Rao and F. Matos. *Analgesic and antiinflammatory effects of two chemotypes of Lippia alba: a comparative study*. Pharmaceutical Biology, **36**, 347–351 (1998).
97. M. Rinaldi, M. Caffo, L. Minutoli, H. Marini, R.V. Abbritti, F. Squadrito, et al. *ROS and brain gliomas: an overview of potential and innovative therapeutic strategies*. International Journal of Molecular Sciences, **17**(6), 984 (2016).
98. N. Frighetto, J.G. de Oliveira, A.C. Siani and K.C. das Chagas. *Lippia alba Mill NE Br. (Verbenaceae) as a source of linalool*. Journal of Essential Oil Research, **10**, 578–580 (1998).