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Review

Central nervous system and analgesic profiles of *Lippia* genus

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ABSTRACT

Many people use medicinal plants to relieve disorders related to the central nervous system, such as depression, epilepsy, anxiety and pain, even though the effectiveness of most of them has not yet been proven through scientific studies. Plants of the *Lippia* genus, Verbenaceae, are widely used in ethnobotany as a food, for seasoning and in antiseptic remedies. They are also marketed and used for the treatment of different types of pain, including stomach ache, abdominal pain and headache, as well as being used as sedatives, anxiolytics and anticonvulsants. Despite their widespread use, there are no reviews on the central nervous system profile of plants of this genus. Therefore, the databases Medline-PubMed, Embase, Scopus and Web of Science were searched using the terms *Lippia* and biologic activity. Thirty-five papers were found. Eleven species of Lippia showed central nervous system activity, with leaves and the aerial parts of plants being the most commonly used, especially in aqueous and ethanol extracts or volatile oil. The species are composed mainly of terpenoids and phenylpropanoids, including polyketides, flavonoids and in less quantity some alkaloids. Although several species of *Lippia* present analgesic activity, most studies have not explored the mechanisms responsible for this effect, however, there is some evidence that volatile oils and constituents of the extracts may be responsible for the relief of some CNS disorders, but the effects on pain modulation seem to be the most exploited so far.

Introduction

The genus *Lippia* belongs to the family Verbenaceae and comprises about 250 herbaceous species of shrubs and is widely distributed all over Central and South America, as well as tropical Africa (Terblanché and Kornelius, 1996; Aguiar and Costa, 2005). The species are distributed in the arid regions of the southwestern United States of America, in the deciduous tropical forests of Central America and in the tropical savannas ('cerrados') of Brazil, which are the regions with high indexes of endemism (Salimena, 2002). Among the prominent examples we can highlight the *L. origanoides*, which is popularly known as 'oregano' in Mexico, and is recognized in the Mexican Pharmacopeiaas a substitute for common 'oregano' (*Origanum vulgare*). It is, therefore, widely used as a condiment in the kitchen and in the preparation of several dishes (Oliveira et al., 2006). The dried and milled leaves of some *Lippia* sp., or the flowers and fruits of this genus have been used as a substitute for *Thymus vulgaris* (another species known as 'oregano') in spice mixtures for pizzas and meats (Lorenzi and Matos, 2002; Santoro et al., 2007).

Brazil is considered to have the largest number of known species (Arthur et al., 2011) represented by species conspicuous by their appearance during the short flowering phase and also by their generally strong and pleasant fragrance (Bezerra et al., 1981). These features make the use of this genus very widespread, ranging from in food preparation as a spice/herb, in cosmetics, as well as in traditional medicine due to it being linked to a range of analgesic, anti-inflammatory, antipyretic, antihypertensive and antimicrobial properties, as well as having beneficial actions in relation to gastrointestinal conditions, menstrual symptoms, pain, migraine and respiratory disorders (Pascual et al., 2001). Moreover, the *Lippia* genus has shown to be of relative economic importance due to the different uses of its volatile oils and the many medicinal uses

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of different species (Salimena, 2002), including their importance for veterinary medicine and agriculture (Soares and Tavares-Dias, 2013).

Due the great medicinal and economic importance of plants and their wide distribution across the regions of the country, the Brazilian government produced the National List of Medicinal Plants Aimed by the Public Health System (SUS – *Sistema Único de Saúde*), a list of vegetal species already used in traditional medicine which have potential to generate products that could be relevant to the Public Health System. *L. origanoides* was included in this list due to its pharmacological properties and its possible use in the development of new pharmaceutical products, including medicaments (herbal medicines) and adjuvants (Ministério da Saúde, 2009).

Among the biological effects reported for the genus *Lippia*, its central nervous system properties are highlighted by a number of studies (Bezerra et al., 1981; Pascual et al., 2001; Mamun-Or-Rashid et al., 2013). As the genus includes many aromatic plants rich in volatile oils their pharmacological properties are commonly attributed to these oils. They are largely comprised of terpene compounds which have already been shown to have clinical applicability and are part of various drugs (Guimarães et al., 2013, 2014; Gouveia et al., 2017).

This study aims to examine research in relation to the use of species of the *Lippia* genus directed to conditions related to the CNS. This will hopefully help to promote improvements in methodological and theoretical methods; identify trends, overlaps and gaps in research; as well as clarifying and summarizing the main existing works. Other studies of this nature have been described in the literature, however, there has been no systematic review focused on the correlation between the pharmacological effects and the chemical composition of the plants and their influence on the CNS (Terblanché and Kornelius, 1996; Pascual et al., 2001; Catalan and De Lampasona, 2002; Hennebelle et al., 2006, 2008; Oliveira et al., 2006; Ombito et al., 2015).

Many studies just describe the use of plants of this genus in traditional medicine, often with contradictory results, or only their use in food or as raw material. Therefore, considering the importance of this plant genus and the absence of systematic reviews of its pharmacological importance through preclinical studies, we carried out this extensive systematic survey in order to support translational studies and/or new preclinical studies.

Search strategy

Four digital databases, Medline-PubMed, Embase, Scopus and Web of Science were used to search for studies that met the inclusion criteria: preclinical animal-model studies of CNS pharmacological studies of *Lippia* species. The database search was performed in the period up to March 30, 2018 using the MesH and free search terms *Lippia* and biologic activity. The search strategy structure was designed to include any study published that assessed the pharmacological pre-clinical profile of the *Lippia* species. The search was limited to animal-model studies. There was no contact with researchers and/or attempts to identify non-published data.

All the electronic titles found, selected abstracts and complete texts from articles were revised independently by at least two reviewers (JSSQ, PSSL). Discrepancies over the inclusion/exclusion of studies were solved with a consensus meeting. Studies in humans, literature reviews, editorials/letters, case reports, and isolated substances were excluded. The information extracted included data on the *Lippia* species, the part of the plant used, their main compounds, type of animal used, model of study and key findings.

Outcomes

A total of 3817 abstracts and citations were electronically identified in the first search. After the exclusion of duplicate articles and the triage of relevant titles and abstracts, 776 titles were included in our list for analysis, trying to identify studies that evaluated *Lippia* that met our inclusion criteria. Thirty five articles met the inclusion/exclusion criteria previously established and were included in our review.

The search of the databases showed that studies related to the genus *Lippia* included a broad range of species, with 27 different ones being the subject of research for different purposes This alone confirms the importance of the ethnopharmacologicali study as a basis for initiating preclinical studies. The areas of interest found in the articles are mainly phytochemical studies, CNS disorders, pain and inflammation. Our survey identified the following nine plant species as being the subject of research in studies: *L. alba, L. multiflora, L. gracilis, L. grata, L. origanoides, L. graveolens, L. geminata, L. origanoides*, and *L. adoensis.* So, the number of species studied is still very small in relation to the number of species of the genus, which reinforces our argument that more studies of this important genus are required.

We found that the parts of the plants mainly used in the experimental protocols in the studies were leaves and aerial parts, particularly as aqueous and ethanol extracts or volatile oils. The part of the plants used is similar to that found in ethnopharmacological studies, which shows that they are primarily used in infusions that require the leaves and aerial parts (Oliveira, 2004; Hennebelle et al., 2008; De Carvalho Nilo Bitu et al., 2015). As we expected, due to the presence of many aromatic plants in the genus which are used for the treatment of diseases, studies with volatile oil, mainly terpenoids and phenylpropanoids, with some polyketides and in less quantity some alkaloids, predominate in our survey (36%) (De Sousa, 2011).

Many VO mainly comprising terpenes whose various activities and mechanisms of action have already been well described in the literature were found. The studies identified do not state if the presence of terpenes influenced the selection of these mixtures (VO) for pharmacological evaluation by the authors. However, we hypothesize that this may well be the case given the number of studies which support the idea that VO are pharmacologically interesting because of the presence of terpenes (Guimarães et al., 2013; Lillehei and Halcon, 2014; De Cássia da Silveira e Sá et al., 2017). Studies investigating its applicability in diseases that cause pain, inflammation, oxidative stress imbalance and CNS disturbances are common (Dobetsberger and Buchbauer, 2011; El Hadi et al., 2013; Ali et al., 2015). Moreover, terpenes has demonstrated strong bioactivity on the modulation of cytokines and in the inflammatory process, central nervous system activity, pain and nerve sensitization, among other interesting pharmacological targets (González-Burgos and Gómez-Serranillos, 2012; Quintans et al., 2019; Santos et al., 2019).

Most of the studies performed an extensive phytochemical analysis to describe the main compounds (terpenoids: carvacrol, *p*-cymene, *o*-cymene, thymol and *E*-caryophyllene, and others chemical classes, such as flavonoids, phenolic acid, and alkaloids) (Box 1).

Terpenes and terpenoids are the primary constituents of the VO of many types of medicinal plants and flowers. They are derived biosynthetically from units of isoprene, which has the molecular formula C_5H_8. Terpenes are chemical entities having low molecular weight and usually low water solubility. They can penetrate the blood-barrier and produce their effects, anxiolytic, sedative and anticonvulsant, on the CNS (Quintans-Júnior et al., 2008; De Sousa, 2011). The articles found in our review highlighted action on the CNS through the GABAergic pathways, which corroborated the pharmacological evidence of the anxiolytic, sedative, myorelaxant

Box 1
Studies on CNS and analgesic profiles of *Lippia* genus.

Authors, year, Country	Extract and part of the plant	Majority compounds	Models of study	Animals (strain/sex)	Dose (mg/kg)/route	Key findings
Lippia alba						
Costa et al., 1989, Brazil	Ethanolic extract/leaves	NR	Analgesic	Mice (*Swiss*/F)	50 mg/ml *p.o.*	Significant analgesic effect in screening test
Viana et al., 1998, Brazil	EO/leaves	I citral II carvone	Analgesic	Mice (*Swiss*/F)	0.5, 1, 2, 10/*i.p.* and *p.o.*	Both chemotypes present analgesic effects and only EO I was reversed by the opioid antagonist (naloxone)
Vale et al., 1999, Brazil	EO/leaves	I citral (55.1%) β-Myrcene (10.5%) II citral (63.0%) Limonene (23.2%) III carvone (54.7%) Limonene (12.1%)	Anxiolytic	Mice (*Swiss*/M)	25=200/*i.p.*	Anxiolytic effect from three chemotypes. However, a more potent activity was presented by EO II which showed a significant effect with a lower dose
Viana et al., 2000, Brazil	EO/leaves	β-Myrcene Citral Limonene	Anticonvulsant	Mice (*Swiss*/F)	100, 200, 400/*i.p.*; *p.o.*	The constituents of the EO present a pharmacological profile similar to that shown by DZP-like drugs and are responsible, at least in part, for the anticonvulsant effect
Zétola et al., 2002 Brazil	Ethanolic extract/leaves	Flavonoid	PTB-induced sleep Anticonvulsant	Mice (*Swiss*/M)	200/*p.o.*	Extracted in ethanol 80% (v/v), presents sedative and myorelaxant effects and this presents the highest flavonoid content.
Neto et al., 2009, Brazil	Ethanolic extract/leaves	I linalool (77.95%) II geranial (33.49%) Myrtenyl acetate (23.4%) III geranial (35.98%) Myrtenyl acetate (25.58%)	Anticonvulsant	Mice (*Swiss*/M)	300/*i.p.*	Anticonvulsant properties might be correlated to the presence of a complex of non-volatile substances phenylpropanoids, flavonoids and/or inositols, and also to the volatile terpenoids which have been previously validated as anticonvulsants.
Hatano et al., 2012, Brazil	EO/leaves	Carvone (54.17%) Limonene (23.13%)	Anxiolytic	Rats (*Wistar*/M)	25/*i.p.*	Repeated treatment exerts anxiolytic-like effects
Heldwein et al., 2012, Brazil	EO/leaves	Linalool (59.66%) 1,8-Cineole (9.11%)	Potentiation with BDZ/Reversal of anesthetic effects	Fishes (Silver catfish/–)	50, 100, 300 μl/l	Anestheticeffects of the EO were reversed sooner by flumazenil, suggesting the involvement of the GABAergic system
Haldar et al., 2012, India	PELA, CELA, EELA, AELA/leaves	Phytosterol, alkaloid, flavonoid, phenolic compound, saponin	Analgesic	Rats (*Wistar*/M)	460, 500/*p.o.*	AELA has a potent analgesic effect probably due to the presence of flavonoids in its composition
L. multiflora						
Abena et al., 1998, Congo	Aqueous extract/leaves	NR	Analgesic	Rats (*Wistar*/F,M)	200, 400, 600/*i.p.* or *p.o.*	Possess tranquilizer and analgesic activities similar to Diazepam
Abena et al., 2001, Congo	Aqueous extract and EO/leaves	NR	Spontaneous motor activity PBT-induced sleep Analgesic	Rat (*Wistar*/F,M)	2 ml/kg *p.o.*	The results confirm the tranquillizer and analgesic activities and reveal that the crude extract would be more of a muscle relaxant and the volatile oil more an analgesic
Abena et al., 2003, Congo	EO/leaves	*p*-Cymene (41.1%) Thymol (19.0%) Thymylacetate (14.2%)	Analgesic	Mice (*Swiss*/M)	2, 4 and 8 ml/kg *p.o.*	Monoterpenes, as the major constituents of volatile oil of *L. multiflora*, possesses analgesic and antipyretic activities
Jigam et al., 2009, Nigeria	Crude extract/leaves	Alkaloids, flavonoids, tannins, saponins, glycosides, volatile oils	Analgesic	Mice (*Swiss*/F,M)	200, 400/*i.p.*	Significant analgesic activity by leaf extracts at the two doses used.
Iwalewa et al., 2007, Nigeria	EO/leaves (emulsion)	NR	Analgesic	Rats (*Wistar*/M)	1.2–4.8/*i.p.*	The lippia oil formulation exhibited a significant dose-dependent analgesic effect, showing peripheral and central activities. Level of the antioxidant markers as possible mechanism of this activity.
Bassoueka et al., 2015, France	Aqueous extracts/leaves	Alkaloids, flavonoids, steroids, tannins	Strychnine-induced convulsion	Rats (Wistar/F, M)	400, 800/*p.o.*	The extract of Lippia multiflora has no significant effect on the parameters studied
L. gracilis						
Mendes et al., 2010, Brazil	EO/leaves	Thymol (32.68%) *p*-Cymene (17.82%), methyl thymol (10.83%)	Analgesic	Mice (*Swiss*/M)	50, 100, 200/*p.o.*	The EO inhibited acid-acetic writhing.

Studies on CNS and analgesic profiles of *Lippia* genus.

Authors, year, Country	Extract and part of the plant	Majority compounds	Models of study	Animals (strain/sex)	Dose (mg/kg)/route	Key findings
Guilhon et al, 2011, Brazil	EO/leaves	Carvacrol (44.43%), o-cymene (9.42%), γ-terpinene (9.16%)	Analgesic	Mice (Balb-c/M)	10, 30, 100/*p.o.*	Antinociceptive effect (not reversed by Naloxone) could potentially be mediated by cholinergic receptors and the nitric oxide pathway.
Guimarães et al., 2012, Brazil	Methanolic extract/leaves	Naringenin	Analgesic	Mice (*Swiss*/M)	100, 200, 400/*p.o.*	Methanolic extract has a therapeutic potential for painful conditions.
Lippia grata						
Siqueira-Lima et al., 2014, Brazil	OE/leaves	Camphor (27.2%), *E*-Caryophyllene (11.6%), camphene (11.3%), bicyclogermacrene (9.4%)	Analgesic	Mice (*Swiss*/M)	6, 12, 24/*p.o.*	EO was capable of reducing the nociceptive face-rubbing in capsaicin, glutamate and both phases of the formalin test. The immunofluorescence protocol demonstrated that the βCD-EO activated important areas in the CNS
Siqueira-Lima et al., 2017, Brazil	OE/leaves	Camphor (27.2%) *E*-Caryophyllene (11.6%) Camphene (11.3%) Bicyclogermacrene (9.4%)	Analgesic	Mice (*Swiss*/M)	6, 12, 24/*p.o.*	Decreased paw withdrawal and muscle threshold. The OE was shown to affect the opioidergic and serotoninergic pathways. Fos protein immunofluorescence showed decreased expression in the dorsal horn of the spinal cord. Docking study showed interaction energies with the alpha-adrenergic and μOpioid receptors.
Lippia origanoides						
Marçal et al., 2006, Brazil	OE/leaves	*p*-Cymene (26.8%) Thymol (21.9%) Myrcene (12.8%)	Analgesic	Mice (*Swiss*/M)	25–400/*s.c.*	The activation of the opioidergic system appears to play a crucial role in the observed antinociceptive effect.
De Morais et al., 2016, Brazil	Ethanol extract/leaves	Isoborneol (14.66%), bornyl acetate (11.86%), α-humulene (11.23%), α-fenchene (9.32%), 1.8-cineole (7.05%)	Analgesic	Mice (*Swiss*/M)	100, 300, 1000/*p.o.*	Crude ethanol extract presented antinociceptive and anti-inflammatory activities
Oliveira et al., 2014, Brazil	Hydroethanolic extract/aerial parts	NR	Analgesic	Mice (*Swiss*/M)	10, 30, 100/*p.o.*	Analgesic activity
Lippia graveolens						
González-Trujano et al., 2017, Mexico	Aqueous extract/leaves	Thymol (33.4%) *m*-Cymen-8-ol (16.37%) Methyl salicylate (10.48%) Carvacrol (6.75%)	Anxiolytic	Mice (CD-1/M)	1, 3, 10, 30/*i.p.*	Exerts anxiolytic-like activity involving many kinds of constituents, mainly the terpenoids and flavonoids
L. geminate						
Forestieri et al., 1996, Italy	Petroleum ether, ethanolic/aqueous extracts/leaves	Flavonoids, saponins, tannins, alkaloids, sesquiterpenes, sterols	Analgesic	Mice (*Swiss*/M, F)	0.5/*p.o.*	Ethanol extract of *L. germinata* showed a significant analgesic activity
L. adoensis						
Makonnen et al., 2003, Ethiopia	Aqueous and ethanolic extracts/leaves	Phenolic acids, flavonoids, glycosides	Analgesic	Mice (in-house bred/M)	400, 600, 800/*p.o.*	Dose-dependent analgesia produced by both aqueous and ethanol extracts.
Debella et al., 2003, Ethiopia	Aqueous and ethanolic extracts/leaves	Phenolic compounds	Analgesic	Mice (in-house bred/M)	400, 600, 800/*p.o.*	Water extract seems to be slightly more potent at low dose
Debell et al., 2005, Ethiopia	Aqueous and ethanolic extracts/leaves	Phenolic compounds	Inducing pyrexia	Mice (in-house bred/M)	50, 100, 200/*p.o.*	Aqueous extract was found to have more potent antipyretic effect than the ethanol extract.

Abbreviations: VO, volatile oil; PELA, petroleum ether extracts; CELA, chloroform extracts; EELA, ethanol extracts; AELA, aqueous extract; NR, not related; PBT, pentobarbital; BDZ, benzodiazepine; DZP, diazepam; M, male; F, female; *i.p.*, intraperitoneal; *p.o.*, orally.

and anticonvulsant properties (Heldwein et al., 2012; Razavi et al., 2017).

Moreover, drugs that enhance GABA-mediated inhibitory transmission, and subsequently affect neuronal repetitive firing, can be of relevance in alleviating several painful syndromes, since they can produce a membrane stabilizing effect on sensory neurons and/or enhance intrinsic analgesic responses (Jasmin et al., 2004; Enna and McCarson, 2006). This evidence may help to explain the fact that most of the studies presented in Box 1 (64%) are studies of the possible effect of plants of this genus on pain management (or simple screening for analgesic drugs, which was the most common type of study described). Obviously, the fact that previous

ethnopharmacological surveys had described the great concentration of terpenes or flavonoids in the *Lippia* genus and their analgesic and anti-inflammatory properties was important in encouraging many research groups to explore this genus (Siqueira-Lima et al., 2014). Additionally, VO and extracts from *Lippia* genus with antioxidant properties, which modulate the inflammatory process by reducing the production of proinflammatory cytokines (such as IL1-β, TNF-α and others) and act on neurotransmission systems that participate in descending pain-inhibitory mechanisms corroborate this search more directed by the researchers (Leyva-López et al., 2016; Siqueira-Lima et al., 2014, 2017).

Our review provides evidence that the *Lippia* genus is rich in flavonoid compounds, at least in the species studied here, the most commonly described being extracts rich in polyphenols (mainly flavonoids) and naringenin, apigenin, nodifloretin A, nodiflorin A, nodifloridin A and others (Box 1). Flavonoids are a class of plant polyphenols that are consumed in the human diet via vegetables, fruits, cereals, spices, and other plant-based products (Pandey and Rizvi, 2009; Jaeger et al., 2017). Flavonoids are probably one of the most important NP due to the potent biological molecules and are already described and used in clinical practice for the treatment of various diseases, as they have a range off antioxidant, anti-inflammatory, analgesic, anxiolytic and anticonvulsant properties (Diniz et al., 2015; Nijveldt et al., 2001).

Lippia species

Lippia alba (Mill.) N.E.Br. ex Britton & P.Wilson, popularly known as “cidreira” (in the south and southeast of Brazil) and “Basula” (in Hindi, in India), is a plant which is present in Central and South America, being recorded in all regions of Brazil (Tavares et al., 2005). *Lippia alba* is a fast growing plant with a mounding habit and round lavender-like blossoms (Haldar et al., 2012). The main pharmacological studies, arising from folk use, found it had varied activities including cardiovascular (Gazola et al., 2004), anticonvulsant (Soares, 2001), sedative, analgesic, bronchodilator (Carvalho et al., 2018) antioxidant and anti-inflammatory (Viana, 1998; Zétola et al., 2002; Hennebelle et al., 2008; Haldar et al., 2012; Hatano et al., 2012), as well as antiulcerogenic effects (Pascual et al., 2001).

The composition of its VO presents quantitative and qualitative variation, leading to its separation into chemotypes according to its major components (de Abreu Matos et al., 1996; Frighetto et al., 1998; Zoghbi et al., 1998; Hennebelle et al., 2008). In Brazil, there are at least three major chemotypes of *L. alba* with a large variation in some terpenoids, especially citral, carvone and linalool; therefore having different pharmacological effects (de Abreu Matos et al., 1996; Yamamoto, 2006; Linde et al., 2016).

The remarkable action of this plant species on the CNS was characterized by the presence of nine articles demonstrating biological activities typically involving the central pathways, including analgesic (with a central component), sedative, anticonvulsant and anxiolytic effects. Viana et al. (1998) compared the analgesic and anti-inflammatory effects of the VO from the leaves of two chemotypes: “citral” (type I) and “carvone” (type II). The antinociceptive effect was more consistent and marked in the type II, but this effect was not reversed by naloxone (an opioid antagonist). A central analgesic effect was also evident with type I (rich in citral). Interestingly, Gonçalves et al. (2008) and Quintans-Junior et al. (2011) demonstrated the central analgesic effects of carvone and citral with no involvement of the opioid system, but with possible participation of blocking Na^+-channels and the GABAergic system, respectively. In addition, the anti-nociceptive action of citral was found to involve significant activation of the $5\text{-}HT_{2A}$ serotonin receptor (Nishijima et al., 2014). Sousa et al. (2015) showed that VO of *Lippia alba* and its main constituent citral block the excitability of rat sciatic nerves.

Haldar et al. (2012) reported that flavonoids in an aqueous extract of *L. alba* have analgesic and anti-inflammatory effects, which they attributed to the presence of polyphenol compounds that inhibited the enzyme cyclooxygenase and subsequently inhibited prostaglandin synthesis.

The most striking CNS effects for this plant are sedative, anticonvulsant and anxiolytic. The anticonvulsant activity of *L. alba* (type I, “citral”) has been demonstrated in classic screening tests for new antiepileptic drugs (Neto et al., 2009). Citral is a sedative and anticonvulsant compound that produces its effects through, at least in part, the involvement of the GABAergic system, but its effect on the stabilization of the neuronal membrane and the blockade of families of ion channels act synergistically (Stotz et al., 2008; Quintans-Júnior et al., 2010).

The anxiolytic effect studied elucidate a possible GABAergic action and it is believed that this action is related to the presence of non-volatile substances (phenylpropanoids, flavonoids and/or inositols), and also to volatile terpenoids (myrcene, citral, limonene and carvone), which have been previously shown to have anticonvulsant and anxiolytic properties (Viana et al., 2000; Zétola et al., 2002; Neto et al., 2009; Zhu et al., 2014).

In fact, much of the pharmacological evidence relating to *Lippia* genus, including *L. alba*, is strongly associated with the presence of terpenes (mainly monoterpenes) with remarkable action on the CNS (Passos et al., 2009; Guimarães et al., 2013, 2014; Quintans-Júnior et al., 2013; Pina et al., 2017; Habtemariam, 2018).

Lippia multiflora Moldenke, popularly known as “chá-de-gambia”, is a species widely used as an infusion in Africa. Traditionally, its leaves are used as a hot beverage (tea) to treat fever, gastrointestinal disturbances, enteritis, and coughing (Adesina et al., 1995). The VO isolated from its leaves and flowers contains *p*-cymene, thymol and carvacrol (Abena et al., 2003), which have been attributed analgesic and antipyretic activities. Iwalewa et al. (2007) demonstrated a decrease in the plasma level of both nitric oxide (NO) and malondialdehyde (MDA) that was closely associated with the anti-inflammatory and analgesic activities produced by VO.

p-Cymene and carvacrol produce an analgesic effect by the involvement of descending pain-inhibitory mechanisms; by inhibition of pro-inflammatory cytokines (such as IL1β, TNF-α, IL-4, TGF-β, and IL-17), by enhancement of anti-inflammatory cytokines (IL-10), and by involvement of the opioid system (Lima et al., 2013; Guimarães et al., 2014; De Santana et al., 2015; Kianmehr et al., 2016). Thus, these terpenes seem to be key to the effects of VO from *L. multiflora*.

The pharmacological activity of the aqueous extract of *L. multiflora* was assessed by Abena et al. (1998) who concluded that it had tranquilizer and analgesic profiles. However, comparing the extract and VO to confirm the previous activities, the study suggested that the crude extract produced more muscle relaxant effects and the VO was more analgesic (Abena et al., 2001). The phytochemical screening of its crude extract demonstrated the remarkable presence of alkaloids, tannins, flavonoids and saponins (Valentin et al., 1995; Oladimeji et al., 2001). Although not an outstanding feature of the crude extract, the significant analgesic and anti-inflammatory effects were attributed to the presence of alkaloids (Jigam et al., 2009).

Moreover, some of the most important monoterpenes found abundantly in *L. multiflora* volatile oil inhibited allergic inflammation by the modulation of inflammatory cytokines (Lima et al., 2013; Pina et al., 2018), which are synthesized within the CNS by glial cells and neurons, and have modulatory functions on these same cells via interactions with specific cell-surface receptors contributing, at least in part, to the central effects of terpenes and similar compounds (Benveniste, 1998; Cho et al., 2017).

Lippia gracilis Schauer ("alecrim-da-chapada") is a shrubby aromatic species that is distributed in the Brazilian Northeast with a high occurrence in the states of Bahia, Segipe and Piauí. It is probably one of the most popular *Lippia* species in the Brazilian Northeast due to its medicinal properties and food application (Albuquerque et al., 2012). The VO of *L. gracilis* is composed mainly of mono- and sesquiterpenes, and the main compounds are *p*-cymene, γ-terpinene, carvacrol and thymol (Pessoa et al., 2005; Neves et al., 2008; Silva et al., 2008; Mendes et al., 2010; Teles et al., 2010; Guilhon et al., 2011).

As already described here and reinforced in the excellent reviews published by De Sousa (2011), De Cássia Da Silveira E Sá et al. (2013) and Guimarães et al. (2013, 2014) the analgesic and anti-inflammatory profiles produced by the VO are attributed to the presence of terpenes. They act by inhibiting inflammatory mediators, such as cytokines, and reducing neuronal excitability in certain CNS areas.

Studies point out that thymol (another important compound found in VO) modulates voltage-dependent Na^+-channels (Haeseler et al., 2002), K^+-channels (Elliott et al., 1997), GABA A receptors (Mohammadi et al., 2001), α and β-adrenergic receptors (Beer et al., 2007), as well as being related to prostaglandin synthesis (Anamura et al., 1988), which together may contribute to the control of painful sensations produced by this terpene.

The antinociceptive profile of *p*-cymene, the main compound from *L. gracilis* VO, was assessed in animal models of pain in respect of contortions induced by acetic acid, the formalin test and hot-plate test. It has also been reported to have an anti-inflammatory effect (Bonjardim et al., 2012). Moreover, Santana et al. (2011) reported an antinociceptive effect through the opioid system which corroborates other studies that describe the effects of this terpenoid on the CNS, due to, among other factors, its antioxidant profile (Oliveira et al., 2012, 2015).

Furthermore, the analgesic profile of carvacrol has already been described consistently in a number of papers and patents for new drugs or pharmaceutical products (Guimarães et al., 2014; Suntres et al., 2015; Oliveira et al., 2016). The effects of the VO of *L. gracilis* are attributed to its anti-inflammatory actions, rather than to its profile on the CNS. Carvacrol is able to block the recruitment of neutrophils, to reduce the release of IL-1β, TNF-α and NO, and enhance levels of IL-10, resulting in a decrease in the production of inflammatory factors and block hyperalgesic behavior (Guimarães et al., 2010, 2012; Lima et al., 2013; Pina et al., 2017). It was also able to regulate COX-2 expression through its agonistic effect in PPARγ (Hotta et al., 2010). Controversially, some authors attribute the effect on the opioid system, but these data are contradictory in different articles and no evidence of direct involvement of the opioid system in the analgesic effect of carvacrol has been found (Guimarães et al., 2010; Cavalcante Melo et al., 2012).

Additionally, the monoterpenes found in the VO are extensively described as analgesic and its lipophilic characteristics and molecular size facilitates both its passage through the blood brain barrier, to produce local actions such as in relation to oxidative balance, to manage the production of inflammatory factors (such as cytokines) and to directly block ion channels (Abena et al., 2003; Mendes et al., 2010; González-Burgos and Gómez-Serranillos, 2012; Guimarães et al., 2013; 2014; Gouveia et al., 2017; Pina et al., 2017).

Guilhon et al. (2011) also investigated the mechanism of action producing the analgesic behavior of the VO of *L. gracilis*. The authors clearly indicated the involvement of cholinergic receptors in this process (as atropine inhibited the antinociceptive effect) and the involvement of the opioid system (by antagonism produced by naloxone). However, the different chemotypes may elicit significantly different biological responses as reported by Mendes et al. (2010) (thymol – major component) and Guilhon et al. (2011) (carvacrol – major component). Chemotypes of *Lippia* species with their different chemical profiles are equally interesting for comparative study, since the difference in concentrations of the major compounds is an area that should be better explored by drug manufacturers.

Another monoterpene presents in these oils, the γ-terpinene, was evaluated by Passos et al. (2015); the authors demonstrated that γ-terpinene antinociception was inhibited in the presence of naloxone, glibencamide, atropine and mecamylamine, suggesting that this antinociceptive effect in models of chemical nociception was produced through the cholinergic and opioid systems. These effects reflect the previously described pharmacological profile of the major terpenes of VO which has a more complex, complete and therapeutic action than the isolated terpenes.

The therapeutic effects on the CNS of thymol and carvacrol (the main compounds of VO from *L. gracilis*) are related (directly or indirectly) to their anti-inflammatory and antioxidant properties, being difficult to dissociate from it (Suntres et al., 2015; Parsaei et al., 2016). Carvacrol and thymol have potent antioxidant potential, and probably exert a protective action against free radicals, as well as inhibiting superoxide and superoxide-derived reactive species. This is an attractive strategy to control the peripheral and central sensitization associated with several painful states or to improve the neuronal functions of neurotransmission systems in the control of anxiety, depression as well as reducing the *status epilepticus* (defined as continuous convulsions lasting more than 30 min). Additionally, terpenes seem to act directly as antioxidants through free radical scavenging mechanisms and/or as indirect antioxidants by enhancing antioxidant status (enzymatic and non-enzymatic) (González-Burgos and Gómez-Serranillos, 2012). Thus, the characteristics of these two monoterpenes associated with the other terpenes present in the VO from *L. gracilis* (or other VO from *Lippia* sp. rich in terpenes) must be acting synergistically to produce their main biological properties.

Lippia origanoides Kunth is popularly known in Brazil as "alecrim-pimenta" ("pepper-rosemary"), and is native to the north-eastern region of Brazil and north of the state of Minas Gerais (Brazil). This species was called *L. sidoides*, but recently it was renamed as *L. origanoides* which has made it difficult to search for articles in the bibliographic databases, however, it remains an attractive species for pharmacological study. In folk medicine, this aromatic species is used as an antiseptic and antimicrobial (Veras et al., 2017) and is usually applied topically on the skin, mucous membranes, mouth, and throat, or used for vaginal washings (De Oliveira et al., 2014).

Similarly to other *Lippia* species, the crude extract of *L. origanoides* presented antinociceptive activity, mainly in screening tests such as acetic acid-induced writhing and formalin tests, but not in tests involving a greater participation of the CNS component, such as the tail flick test (de Morais et al., 2016). This profile, more oriented to the anti-inflammatory properties seems to be related to the presence of polyphenols in the extract (Lima et al., 2016). The major constituents of the VO of *L. origanoides* are *p*-cymene, thymol and myrcene and demonstrated an analgesic profile in chemical and thermal pain in pre-clinical models. The activation of the opioidergic system appears to play a crucial role in the observed analgesic profile produced by the VO (Marçal et al., 2006). As suggested for other species of *Lippia*, the presence of *p*-cymene (Santana et al., 2011; Quintans-Júnior et al., 2013) and myrcene may involve the mediation of endogenous opioids and α-adrenoreceptors (Rao et al., 1990), as well as an increase in cGMP mediated by stimulation of the arginine-NO-cGMP (Duarte et al., 1992). de Morais et al. (2016) suggested that the chemical composition of VO of *L. origanoides* is variable (depending on the chemotype), therefore this should drive the main biological potentialities, being a pivotal factor for the beginning of the study with this species.

Recently, some new approaches using nanotechnology and encapsulation of drugs have shown promising results following the incorporation of different VO, including some from the *Lippia* species (Quintans-Júnior et al., 2016, 2018; Siqueira-Lima et al., 2017). For example, Botelho et al. (2016) demonstrated that a nanostructured thymol gel (the main compound obtained from *L. origanoides*) was able to provide a significant MPO decreasing in gingiva tissue confirming it to be effective in reducing gingival inflammation in this model. The authors reported that this reduction in the inflammatory process (with the reduction of pro-inflammatory cytokines) contributed to the reduction of pain.

Lippia grata Schauer is a native bush of the semi-arid area of Northeastern Brazil and is used in folk medicine to treat pain and inflammation, but is poorly described in the scientific literature with few reports, especially in relation to its pharmacological effects (O'Leary et al., 2012). The leaf VO demonstrated antispasmodic activities attributed to the presence of carvacrol and thymol (Craveiro et al., 1981; Santos et al., 2011).

Siqueira-Lima et al. (2014) identified a very different phytochemical profile of the VO of *L. grata* than that described by Craveiro et al. (1981), using gas chromatography–mass spectrometry (CG/MS) analysis, they demonstrated the main compounds of this VO to be: camphor, *E*-caryophyllene, camphene, and bicyclogermacrene. Different chemotypes of Verbenaceae (mainly from the *Lippia* genus) can produce different VO phytochemical profiles and, in addition, the time of the year and the place where the botanical specimen was collected can affect this profile. Consistent techniques in the collection and identification of VO are essential for their standardization from an industrial perspective (Craveiro et al., 1981; Tavares et al., 2005). In fact, identifying individual chemotypes is essential in choosing the VO that is most appropriate to the aim of the study. Studies that are guided with support from chemistry professionals who are able to identify these chemotypes are more likely to be successful in their assessment of the CNS properties of *Lippia* species.

The effect of OE on orofacial pain in animal models was evaluated because of the common clinical challenges for orofacial pain management. The authors used an approach involving VO complexed with β-cyclodextrin (β-CD) (used to improve the water solubility and bioavailability of VO). Cyclodextrins have been shown to be an important tool for improving the analgesic effect of OE (Siqueira-Lima et al., 2014, 2016). The use of β-CD in this case helped the VO to produce a stronger antinociceptive activity. The authors demonstrated the involvement of both descending pain-inhibitory mechanisms and CNS areas that contribute to controlling pain, such as the periaqueductal gray (PAG), *Locus coruleus*, rostral ventromedial medulla (RVM) and the nucleus raphe magnus, in the attenuation of orofacial pain by VO. These CNS areas appear to be modulated whenever terpenes and/or VO act on the descending pain suppression pathway (Nascimento et al., 2014; Quintans-Júnior et al., 2016, 2018; Araújo-Filho et al., 2017; Santos et al., 2018). Therefore, the chemical characteristics of terpenes present in VO from *Lippia* species seems to be pivotal for the variability of effects produced by them on the CNS. Their ability to easily pass through the blood–brain barrier (which seems to be common to most terpenes) makes them attractive targets to explore in various central disturbances (Kam et al., 2012).

Moreover, Vogt-Eisele et al. (2007) demonstrated that some monoterpenes (such as camphor) activated TRPV3 receptors, which have been implicated in hyperalgesia, inflamed tissues and possibly skin sensitization, and inhibited several related TRP channels, including ankyrin-repeat TRP 1 (TRPA1) (Waning et al., 2007; Xu, 2005). Another terpene, β-caryophyllene, acts on CB2 receptors whose activation can produce a direct antinociceptive response by causing the release of mediators from non-neuronal cells that alter the responsiveness of primary afferent neurons to noxious stimuli (Ibrahim et al., 2005). β-Caryophyllene is one of the terpenes with a profile acting on CNS areas that modulate the descending pain suppression pathway, at least when evaluated in a chronic non-inflammatory widespread pain animal model (a rodent fibromyalgia-like model) (Quintans-Júnior et al., 2016, 2018). Recently, VO of *L. grata* complexed with βCD enhanced the pharmacological efficacy of the VO and produced a longer-lasting analgesic activity. The presence of β-caryophyllene was considered by the authors to play a key role in the pharmacological effect (Siqueira-Lima et al., 2017). The authors pointed out that the VO was antagonized by naloxone and partially antagonized by methysergide, but was not antagonized by yohimbine, thus suggesting that the anti-hyperalgesic effect produced by VO is related to the opioid and serotonergic systems. These features of VO are essential for the development of new proposals for the management of chronic pain, especially in relation to 'dysfunctional pain' which are neglected by the drugs currently used (Nagakura, 2015; Oliveira et al., 2017).

Lippia adoensis Hochst. was cited in two Ethiopian studies whose objective was to screen for the analgesic properties of this and other plants in an attempt to validate their traditional uses. With local names such as "kessie" or "kusaye", this shrub is found in different regions of Ethiopia at an altitude between 1600 and 2200 m above sea level (Debella et al., 2003; Makonnen et al., 2003). Pre-clinical studies using screening tests to assess analgesic effects, such as the acetic acid-induced abdominal constrictions (Debella et al., 2003) and tail flick, hot plate and tail-pinch tests (Makonnen et al., 2003) have revealed that the extract produced an analgesic profile. The presence of phenolic compounds as major chemical constituents may contribute to the analgesic effect, however, the authors themselves acknowledge that the mechanisms of analgesia produced by the extracts need to be investigated further.

Final comments

Our review discussed *Lippia* species being investigated in preclinical animal studies that showed significant medicinal properties in relation to the CNS and that could be important in the control of pain. We chose this approach due to the wide spectrum of plants of this genus that are used for medicinal purposes. However, clinical studies are very rare making systematic reviews very difficult. We therefore chose a more fruitful approach, searching for preclinical studies. We imagine that in the near future it will be possible to carry out systematic reviews of the results of clinical studies, as government institutions (as is happening more in Brazil) start to support the development of herbal medicines from plant species such as *L. origanoides* (formerly known as *L. sidoides*). Translational studies are urgently required to validate the biological effects found in preclinical studies and especially to corroborate the widespread use of these traditional medicinal plants.

Although several species of *Lippia* present activities on the CNS, the central analgesic effects are the most commonly described. However, most studies have not explored the mechanisms responsible for the effects observed and also have not identified the inflammatory mechanisms involved in the processes, the participation of specific neurotransmission systems or the CNS regions involved. Therefore, the majority of studies carried out are speculative in their conclusions about CNS effects, as there are few studies with a molecular approach and with a deep phytochemical study of the species. Thus, this is an essential problem that needs to be solved if research is to translate these results into clinical studies with humans.

Another worrying aspect of the pharmacological studies made using *Lippia* genus is that there are few preclinical reports with chronic models that explore toxicity and/or the therapeutic safety

of the continuous use of these drugs (extracts or VO). Our survey did not find any in the searched databases, although there may be some but this was not a focus of our review. This represents a gap in knowledge that needs to be filled.

Furthermore, it is known that significant therapeutic properties of plant extracts are due to the combined effects of several secondary metabolites. However, in our opinion, studies with isolated compounds present some important advantages, as isolated compounds from natural sources can be employed as tools in the identification of action mechanisms and can also provide structural molds to obtain synthetic substances, though the capacity of the synergistic effect that usually seems to happen with the use of extracts or VO will be lost. Interestingly, the results with the extracts and the VO were consistent with the majority of ethnopharmacological studies, which corroborated the importance of folk medicine as a kind of guide for preclinical studies. Obviously, a consistent prior phytochemical study, knowledge of the pharmacological properties of major components and a guided scientific approach are key in the study of any natural product seeking to minimize possible false positive results. Moreover, studies with species of the genus *Lippia* need to evaluate its effects in chronic disease models and in long-term treatment in repeated doses.

A modern approach that is still little found in studies with *Lippia* species is the use of pharmaceutical technology, such as nanotechnology, complexation of drugs (such as cyclodextrins) or incorporation in polymers. The traditional approach of testing non-standard extracts or complex mixtures (as VO) may be a limitation in looking for more modern preparations using pharmaceutical technology. These scientific barriers need to be urgently overcome, seeking formulations that guarantee better pharmacological effects, low toxicity and greater effectiveness.

Although the action mechanisms are not completely understood (in most studies), either because of the mainly unspecific animal models used or due to the extracts evaluated (non-standardized and without specific chemical markers) the findings of the articles presented here strongly suggest that *Lippia* species are clinically promising and that its uses in folk medicine are rational and appear to produce important clinical effects (since preclinical studies corroborate these effects). Therefore, there is evidence that the constituents of the extracts and VOs are candidates for the relief of some CNS disorders, such as anxiety and perhaps can act as adjuvant in the treatment of the seizures of epileptic patients, as well as for the management of painful conditions.

Authors' contributions

PSSL, FRSP, JSSQ, AML and AANL contributed with both the survey of the articles and the preparation of the manuscript. IRAM, HDMC, GZ, JSSQ, AML, AANL and LJQJ participated in the drafting, correction and with their expertise in the discussion and finalization of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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