Aloysia gratissima (Gillies & Hook. ex Hook.) Tronc. var. *gratissima*

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A. gratissima var. *gratissima*. (Photo: Risso OA)

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Á. Máthé, A. Bandoni (eds.), *Medicinal and Aromatic Plants of South America Vol. 2*, Medicinal and Aromatic Plants of the World 7,
https://doi.org/10.1007/978-3-030-62818-5_3

Abstract In Argentina and the neighboring countries, the aboveground part of *Aloysia gratissima* (Gillies & Hook. ex Hook.) Tronc. "whitebrush" is used for its aromatic and medicinal properties. The plant is a shrub reaching 3 meters height that is distributed in both South and North America. In Argentina, it is mainly used by the so called "yerba mate" industries, in compound products. As in the case of other native aromatic and medicinal species, the demand is mainly covered by the collection of wild plants, which leads to the possible overexploitation, deterioration of both resources and the heterogeneity of the commercialized product.

Keywords "Usillo" · 1,8-Cineol · Spathulenol · Cadinol · Antispasmodic

1 Introduction

Aloysia gratissima is an aromatic shrub, a close relative of *Aloysia citrodora,* the "lemon verbena". Since pre-hispanic times, it is widely used by traditional popular medicine and is consumed in the traditional South American infusion: "mate" (Martínez 2011; Galli et al. 2015). In the last decades, the demand of the "yerba mate" industry has increased considerably. Numerous works endorse the properties of its secondary metabolites due to which it is consumed (Bucciarelli and Skliar 2007; Berardi 2010; Consolini et al. 2011). Phenotypes of varying chemical composition have been described according to the regions of collection. To date, collection is still the main source of raw material supply (Ricciardi et al. 2006; Trovati et al. 2009; Benovit et al. 2015). It appears possible to select chemotypes of stable chemical composition for use in a variety of products.

2 Taxonomic Characteristics

The *Aloysia gratissima* complex (Verbenaceae) is a group of specific and infraspecific taxa, the limits of which are controversial. Various authors (Troncoso 1964; Botta 1979; Siedo 2006; O'Leary et al. 2012, 2016) have assigned different significance to individual characters in delimiting taxa in the complex, resulting in a variable number of species and varieties recognized over time. Currently, *A. gratissima* (Gillies & Hook. ex Hook.) Tronc. has been delimited in two varieties: *gratissima* and *sellowii,* depending on the qualitative and quantitative characteristics of their leaves. *A. gratissima* var. *gratissima* leaves of smaller, blade length 9.9–19.0 × blade width 3.6–7.3 mm and leaves of *A. gratissima* var. *sellowii* of larger, blade length 20.7–32.4 × blade width 7.7–13.0 mm. Furthermore, the variety "*sellowii"* is distributed only in South America, being frequent in Northern Argentina, in the provinces of Misiones, Corrientes and Salta, and Southern Brazil. It has a more restricted distribution than *A. gratissima* var. *gratissima* (Moroni et al. 2016). Due to the difficulty of the delimitation of species within the complex, numerous synonyms have been assigned to the taxon by different authors, even being included in other genera. Most used synonymies: *Aloysia chacoensis* Moldenke, *Aloysia gratissima* (Gillies & Hook. ex Hook.) Tronc. var. *paraguariensis*, *Aloysia ligustrina* (Lag.) Small var. *paraguariensis*, *Aloysia lycioides* Cham., *Lippia ligustrina* (Lag.) Kuntze var. *paraguariensis*, *Lippia lycioides* (Cham.) Steud., *Verbena gratissima* Gillies & Hook. ex Hook., *Lippia ligustrina* (Lag.) Kuntze var. *lasiodonta*, *Lippia gratissima* (Gillies & Hook.) L.D. Benson, *Aloysia gratissima* (Gillies & Hook. ex Hook.) Tronc. var. *revoluta*, *Aloysia lycioides* Cham. var. *revoluta*, *Aloysia famatinensis* Ravenna.

Nearby species are *Aloysia citrodora* Paláu ("cedrón", lemon verbena) and *Aloysia polystachya* (Griseb.) Moldenke ("té de burro" – donkey tea, "burrito" – little donkey). *A. citrodora* has larger leaves, elliptic-lanceolate sheet 3.5–7.5 cm long. × 1–1.5 cm wide, while *A. polystachya* is a lesser and lax-bearing bush with a tendency to layer naturally, its inflorescences are speciform clusters of 0.5–1.2 (−2) cm long, dense, sessile, solitary or branched of 0.5–1.2 (−2) cm long. White, tiny flowers, arranged in whorls of 4, on the spine; Very broadly obovate bracts, hugging the calyx (Barboza et al. 2006; Elechosa 2009; Múlgura et al. 2012).

3 Crude Drug Used

As a vegetable drug, aerial parts are consumed: leaves, stems and flowers, in infusions (Del Vitto et al. 1997; Barboza et al. 2006; Martínez 2011; Zeni 2011), particularly in "mate", a traditional infusion in the southern region of South America. Hence, the herb industry is an important source of demand. It is mixed with *Ilex paraguariensis* "yerba mate" to produce herb blends (Photo 1). In the central region of Argentina, annually one million kg/year is collected for use in this industry (Galli et al. 2015).

4 Major Chemical Constituents and Bioactive Compounds

The essential oil yield, obtained by hydrodistillation, ranges between 0.15–1.2%, in the different populations studied and varies according to the phenophase of the plant: higher yields were observed when the harvest was carried out in autumn and summer (Ricciardi et al. 2000, 2006; Alonso and Desmarchelier 2015; Risso et al. 2018). It was also found that the maximum production of essential oil is obtained when the plant is grows in full sun (Dos Santos 2007; Pinto et al. 2007). The composition of its essential oil is complex and diverse, with sesquiterpene compounds prevailing in proportion over oxygenated terpenes (Ricciardi et al. 2000). In addition, the composition and percentage of the constituents are markedly modified by the season of the year in which the vegetable is harvested (Bailac et al. 1999;

Photo 1 "Yerba mate", with blend herbs. (Photo: Risso OA)

Duschatzky et al. 2004; Ricciardi et al. 2006; Dambolena et al. 2010), by the part of the plant analyzed and by the place of collection (Table 1). In the northeast of the province of San Luis, in materials collected in autumn, the predominance of sesquiterpenes (S) was detected in the populations located above the valley, while in the mountain areas, the compositions with monoterpenes and sesquiterpenes prevail (M + S). The presence of both profiles in the same population added to the higher performance in essential oils of the M + S profile is indicative of the existence of chemotypes (Risso 2018). Among the main components are 1,8-cineole, in the group of monoterpenes, and cadinol (isomer not identified) and spathulenol for sesquiterpenes. Flavonoids, such as quercetin and hesperidin, were found in decoctions and methanolic extracts of the leaves (Berardi 2010). The flavonoids apigenin 5-hydroxy-7,4′-dimethylether, genkwanin and luteolin 7,3′,4′-trimethylether; the *ent*-kaurane hoffmanniaketone and rutin were isolated from ethanol extracts (Da Silva et al. 2006). As for the aqueous extract, ferulic acid is reported as its main constituent (Zeni 2011; Zeni et al. 2014).

5 Morphological Description

Aloysia gratissima is an aromatic shrub that grows up to a height of 3 meters. It has glabrous stems, gray-white and striated bark. Opposite leaves, sometimes solitary, or more than two per knot; petiole of (0.7-) 2.3 (−6.7) mm, elliptical to lanceolate sheet, of 16.5 × 6.3 mm, obtuse or acute apex, conspicuous lateral venation or not, partially serrated-serrated margin, sometimes revolute (Barboza et al. 2006; Moroni et al. 2016). The flowers, tetramers, are arranged in clusters that resemble spikes up to 10 cm long, lonely or arranged in terminal panicles (Photo 2). The calyx is hairy, with a white corolla, scented, briefly pedicelled with the limbo divided into 4 uneven lobes. It has ovate-elliptical floral bracts, occasionally linear. It blooms numerous times from early spring to late autumn. The fruit is dry, schizocarpic, separated at maturity in two clusters of 1.5 mm, glabrous, each with one seed (Davies 2004; Del Vitto et al. 2011).

Table 1 Qualitative and quantitative variability of the main chemical components of the essential oil of *Aloysia gratissima* according to the part of the plant and the place of collection

Part of the plant	Chemical composition	Harvest location	References
Leaves	Sabinene (30%), β-pinene (8%)	Minas, Uruguay	Soler et al. (1986a)
	trans-pinocamphone (10.9%), *trans*-pinocarvyl acetate (9.3%), β-caryophyllene (6%), germacrene D (4.6%)	Sao Paulo, Brazil	Sartoratto and Augusto (2003)
	Pinocarvyl acetate (17.6%), pinocamphone (16.3%) and guaiol (11.5%)	Lavras, Brazil	Dos Santos et al. (2013)
	1,8-cineole (13.7%), germacrene D (13.4%), β-caryophyllene (12.7%), β-pinene (11.7%)	Guabiruba, Brazil	Santos et al. (2015)
	1,8-cineole (18.5%), sabinene (9.5%), guaiol (6.8%), bicyclogermacrene (5.1%)	Santa Maria, Brazil	Benovit et al. (2015)
	Isopinocamphone (25.4%), limonene (15.1%), guaiol (12.7%)	Sao Carlos, Brazil	Trovati et al. (2009)
	β-Pinene (14.1%), isopinocamphone (18.4%), pinocarvyl acetate (13.5%)	Goiânia, Brazil	Franco et al., (2007)
	Cadinol (isomer not identified) (32–33%), caryophyllene oxide (11–8.6%), β-caryophyllene (4.3–3.3%) and *trans*-verbenol (5.8–2.8%)	San Luis, Argentina	Bailac et al. (1999)
	1,8-cineole (45.5%), sabinene (8.3%), carvacryl acetate (8.2%), spathulenol (8.7%)	La Rioja, Argentina	Dambolena et al. (2010)
Flowers	Pulegone (65.8%)	Córdoba, Argentina	Zygadlo et al. (1995)
	Globulol, sabinene, β-caryophyllene, caryophyllene oxide	Uruguay	Soler et al. (1986b)
	Guaiol (19.5%), germacrene B (10.5%), bulnesol (10%), *β*-caryophyllene (8.9%)	Lavras, Brazil	Dos Santos et al. (2013)
Aerial parts	Pinocamphone (13.5–16.3%), β-pinene (10.5–12%), pinocarvyl acetate (7.3–8.3%) guaiol (6.6–8.7%), bulnesol (3.7–4.1%)	Campinas, Brazil	Silva et al. (2007)
	1,8-cineole (17.6%), guaiol (10.3%), germacrene D (6.2%), bicyclogermacrene (5.6%), β-caryophyllene (5%), δ-elemene (5%), sabinene (4.3%)	Rio de Janeiro, Brazil	García et al. (2018)
	Cadinol (isomer not identified) (17.4%), caryophyllene oxide (15.8%), limonene oxide (5.3%), chrysantenyl acetate (5.6%), β-caryophyllene (4.8%)	San Luis, Argentina	Duschatzky et al. (2004)
	γ-Elemene (20%), globulol (19%), spathulenol (13%)	La Rioja, Argentina	Juliani et al. (2004)

(continued)

Table 1 (continued)

Part of the plant	Chemical composition	Harvest location	References
	β–elemene (tr - 35.7%), viridiflorol (0.9–33.6%), β-caryophyllene (1.8–28%), α-thujone (6.8–17.5%), 10-*epi*-cubebol (0.1–13.4%), bicyclogermacrene (3.8–12.8%), germacrene D (1.9–10.1%)	Corrientes, Argentina	Ricciardi et al. (2006)
	Spathulenol, 1,8-cineole	San Luis, Argentina	Risso et al. (2018)
	β-Thujone (36.1%), α-thujone (32.2%), 1,8-cineol (10.7%), sabinene (6.2%)	Northwestern Argentina	Gálvez et al. (2018)
	Kunzeaol (16.3%), β-caryophyllene (8.5%), cubebol (5.1%), viridiflorol (3.1%), germacrene D-4-ol (3.3%)	Cochabamba, Bolivia	Arze et al. (2013)
	1,8-cineole (22.1%), germacrene D (19.6%), bicyclogermacrene (7.9%)	Uruguay	Davies (2004)

Photo 2 *Aloysia gratissima* inflorescences. (Photos: AO Risso and A Posadaz)

6 Geographical Distribution

Aloysia is an American genus. Its area extends from the Southern United States of America to Central Chile and Argentina. In particular, *A. gratissima* var. *gratissima* has a bicentric distribution (Fig. 1). In North America, it is found in the Southern United States and Northern and Central Mexico. In South America, in Bolivia, Paraguay, the Southern point of Brazil, Uruguay, Northern and Central Argentina and Central Chile.

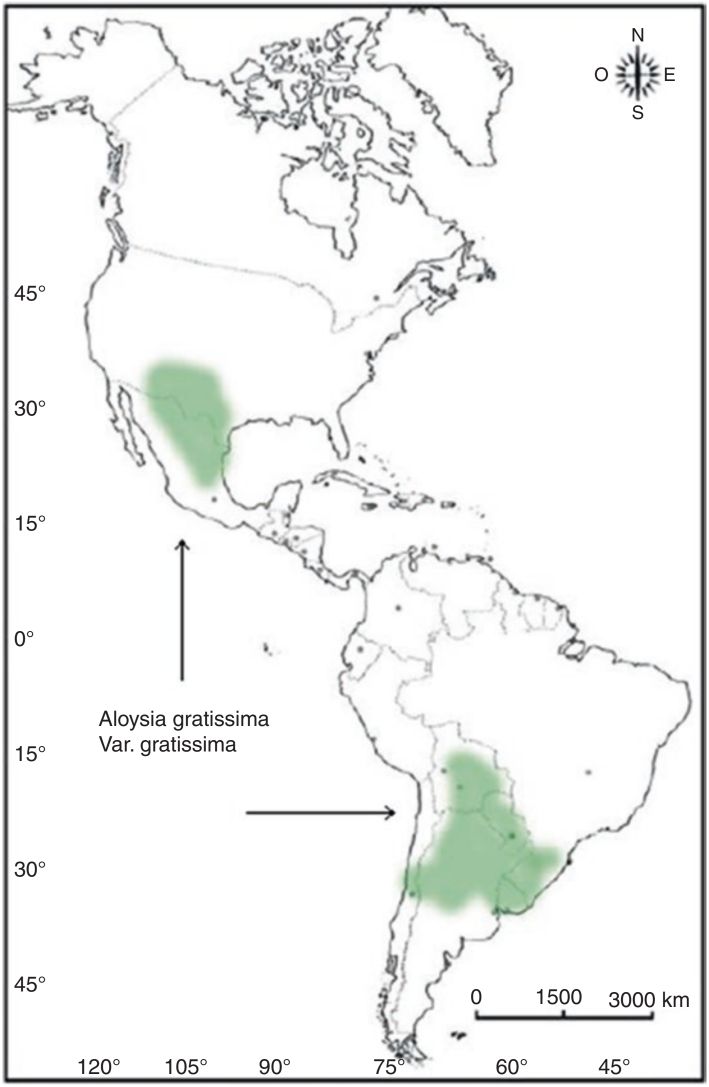

Fig. 1 Geographic distribution *A. gratissima* var. *gratissima.* (Adapted from Moroni et al. 2016)

7 Ecological Requirements

A. gratissima grows in xerophilous environments and dry forests, in Argentina. It is also found in temperate or temperate-warm climate in Paraguay and Uruguay (Álvarez 2019). It also grows in rocky and shallow soils of mountains and clayey and deep plain soils.

The seeds are photoblastic positive. Under controlled cultivation conditions, the total dry phytomass is superior in plants grown in full sun. The thickness of the adaxial cuticle, the palisade parenchyma and the total thickness of the leaf are greater in full sun. Furthermore, under this condition a greater number of glandular trichomes develop on the abaxial surface of the leaves (Dos Santos 2007).

Some recent successes and achievements are the study of the agronomic behavior of the species in Uruguay (Davies 2004), study of ecophysiology; in Brazil (Dos Santos 2007), studies of chemical and morphological variability, and Argentina (Ricciardi et al. 2006; Risso 2018).

8 Traditional Use and Common Knowledge

It is a species with numerous vernacular names, which in part alludes to its wide use throughout its geographical distribution. In Argentina it is known as “usillo”, “palo amarillo” (yellow stick), “niño rupá” (baby’s crib), “azahar del campo”, among others (Del Vitto et al. 1997; Botta 1979; Barboza et al. 2006; Ricciardi et al. 2006; Martínez 2011; Galli et al. 2015; Moroni et al. 2016); in Brazil it is known as “mimo do Brasil” (treat from Brazil), “brazilian-lavender”, “erva santa” (Dos Santos 2007; Franco et al. 2007; Trovati et al. 2009; Zeni et al. 2014), in Uruguay “cedrón del monte” (Davies 2004). Its leaves and stems are cited mainly for their digestive use and to relieve upset stomach, while their infusion flowers are mainly used to relieve bronchial conditions. It is also used to soothe menstrual cramps, against hemorrhoids and to relieve symptoms associated with nervous system disorders. In addition, infusions made with the aerial parts are used to treat varicose veins, dizziness and against hemorrhoids (Alice et al. 1991; Del Vitto et al. 1997; Barboza et al. 2006; Martínez 2011; Zeni 2011; Zeni et al. 2014; Nuñes Gonçalves 2016; Bernasconi Salazar et al. 2017). It is also a species considered ornamental and honey due to its numerous blooms of pleasant aroma (Cardoso 2005; Sérsic et al. 2006).

9 Modern Medicine Based on Its Traditional Medicine Uses

Studies carried out by Berardi (2010) endorse its traditional use as intestinal antispasmodics, since they reduce the spasmogenic effects of acetylcholine. The effects on acetylcholine can be explained by a non-competitive antagonism of the Ca^{+2} influx (Consolini et al. 2011). In addition, tests performed on mice show that orally administered aqueous extract show gastroprotective activity, exhibited significant antiulcer activity (Bucciarelli and Skliar 2007). Zeni (2011), in studies with the aqueous extract (AE), validated its potential use in the prevention or treatment of diseases that involve glutamatergic and serotoninergic systems. The main component of the AE, ferulic acid, was also able to exert an antidepressant effect in mice.

In addition, studies done with infusion on rats show that there is no toxicity due to acute exposure at a dose of 2000 mg/kg (Zeni 2011; Rihl et al. 2017). On the other hand, Ricco et al. (2010) in genotoxicity tests using the alkaline kite technique (Singh et al. 1988), revealed the absence of genotoxicity and a marked antioxidant power in extracts prepared in infusion and cooking (dose 0.05 mg/ml and 0.5 mg/ml). As regards toxic compounds, the presence of germacrene has been documented, whose structure, by oxidation, gives rise to a series of lactone-type compounds that may produce allergic or cytotoxic reactions. It also highlights the presence of ketones, such as thujone (Ricciardi et al. 2000) and pinocamphone (Trovati et al. 2009; Benovit et al. 2015), recognized as nerve toxins. Thus, seasonal variations of the major constituents modify the pharmacological applications of the species (Ricciardi et al. 2000, 2006). On the other hand, Benovit et al. (2015) have reported the anesthetic effects of the essential oil and its bioactive fractions on a species of "catfish" used in aquaculture (*Rhamdia quelen*) as an alternative to the synthetic compounds traditionally used. The data obtained for crude extracts and methanolic fractions of *A. gratissima* showed a significant reduction in the intensity of inflammations (Vandresen et al. 2010). Alcoholic, hydroalcoholic and decoction extracts showed selective antibacterial activity (inhibition/inactivation) on bacterial inoculums of *Staphylococcus aureus*, *Rhodococcus equi*, *Enterococcus faecalis*, *Salmonella enteritidis*, *Escherichia coli* and *Pasteurella multocida*. Two extracts showed greater antibacterial activity for *Rh. equi* and *P. multocida,* both bacteria related to cases of pneumonia and other respiratory conditions in humans and animals. In addition, the alcoholic extract of fresh plants showed greater activity, compared to decoctions and extracts of dried plants (Souza and Wiest 2007). Studies carried out by Freires et al. (2015) with essential oils and bioactive fractions on *Streptococcus mutans* and *Candida albicans* highlight the promising antimicrobial activity of this plant and suggest avenues for future translational research on the treatment of dental caries and oral candidiasis. It was observed that the essential oil has antimicrobial properties, especially the fraction corresponding to the inflorescences, against *Candida albicans* and *Streptococcus pneumoniae*, which supports its use in folk medicine in pneumonia and bronchial conditions (Dos Santos et al. 2013). A study done on *Allium cepa* cells shows that the infusion and the essential oil have antiproliferative effects, therefore possessing potential activity against tumor cells (Hister et al. 2009). It was also observed that it has activity against the Junín virus (responsible for hemorrhage fever) and herpes simplex virus type 1 (HSV-1) (García et al. 2003). The antiparasitic activity of the essential oil against *Leishmania amazonensis* has also been reported, with guaiol being the constituent with the highest activity (García et al. 2018). Further, it has antifungal properties against *Ascosphera apis* (Dellacassa et al. 2003), and against *Aspergillus* and *Fusarium* species (Gálvez et al. 2018).

10 Conclusions

A. gratissima is a native plant species of Argentina with a wide geographic distribution. It is used in folk medicine by numerous communities. Scientific studies endorse many of the known properties observed by these communities and explore new attributes. The low genotoxicity of the species strengthens this potential as a medicinal plant (Ricco et al. 2010; Zeni 2011). However, the presence of potentially toxic components has been detected in its essential oils (thujone and pinocamphone) in some wild populations, or in certain phenological states, which should be considered at the time of use or in domestication programs (Ricciardi et al. 2006; Trovati et al. 2009; Benovit et al. 2015). Importantly, the boom in the use of this species by "yerba mate" industries emphasizes the need to study the ways and means of its possible domestication including the selection-breeding of this species. Cultivation and conservation, in the wild, would yield characterized materials for the industries, strengthening a more sustainable and secure marketing chain for consumers.

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