HERBAL MONOGRAPH

Lippia javanica (Burm.f.) Spreng | Verbenaceae

Lippia javanica (Burm.f.) Spreng | Verbenaceae

Synonyms

Lantana galpiniana H.Pearson, *Lippia asperifolia* Rich., *Verbena javanica* Burm.f.[1]

Common Name(s)

Fever tree, lemon bush, wild sage, wild tea (English), '*koorsbossie*', '*koorsteebossie*', '*lemoenbossie*', '*maagbossie*', '*beukesbos*' (Afrikaans), '*mumara*' (Shona), '*musukudu*', '*bokhukhwane*' (Tswana), '*inzinziniba*' (Xhosa), '*umsuzwane*', '*umswazi*' (Zulu), '*umsuzwana*', '*usuzwane*' (Ndebele), '*musutswane*', '*umsutane*' (Swati).[1]

Conservation Status

Least concern, not threatened.[1]

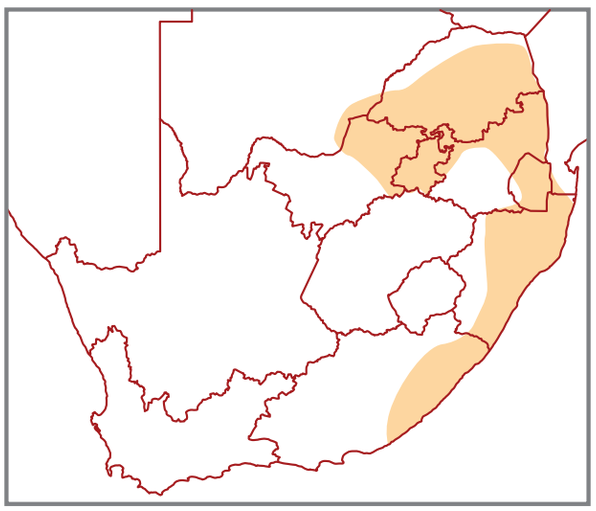
Botany

Lippia javanica (Burm.f.) Spreng belongs to the family Verbenaceae, comprising approximately eight genera and 40 species in southern Africa (Germishuizen et al., 2006). *Lippia. javanica* is a woody, multi-stemmed shrub that grows up to 2 m in height **(A)**. The leaves are 3–4 cm long, hairy on both sides and have dentate, lightly toothed margins. They are rough to the feel with conspicuous veins **(B)**. Leaves are opposite, often in whorls of up to four, and are highly aromatic. The shrub bears dense, rounded flower heads with small flowers that vary in colour from white, cream, yellowish-white to yellow **(C)**. The shrub flowers continuously from February to May and produces small nutlike seeds that are brown in colour (van Wyk et al., 2000).

[1] Red List of South African Plants (redlist.sanbi.org)

Geographical Distribution

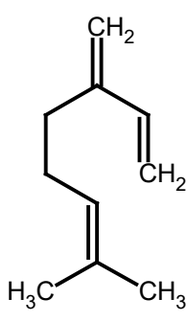
Lippia javanica is a drought-resistant shrub that adapts well to different soil types. It is abundant on hillsides, roadsides, forest edges, stream banks, in grasslands and bushveld. Its natural distribution in South Africa spans the Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga and North West provinces. Its distribution extends to central, eastern and southern Africa including Botswana, Malawi, Swaziland, Mozambique, Tanzania, Zambia and Kenya (Germishuizen et al., 2006; Van Wyk et al., 2000; Retief et al., 1997).



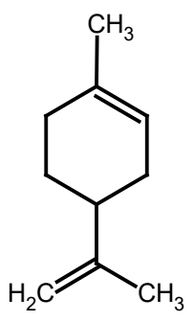
Phytochemistry

Volatile constituents

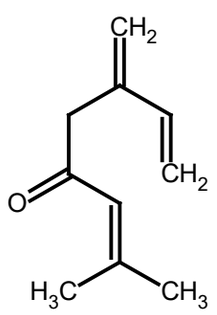
The volatile fraction of *L. javanica* contains various classes of compounds and the profiles vary within and between populations. Generally, the following compounds have been identified in high concentrations in volatile fractions of *L. javanica*; myrcene, myrcenone, β-caryophyllene, carvone, ipsenone, limonene, linalool, ocimenone, *p*-cymene, piperitenone, sabinene, ipsenone, ipsdienone, (*E*)- and (*Z*)-tagetenone (Fujita, 1965, Neidlein et al., 1974; Mwangi et al., 1991, Mwangi et al., 1992, Velasco-Negeureula et al., 1993; Terblanché et al., 1996; Van Wyk, 2008). The oil composition varies considerably within and between populations and five different chemotypes were described by Viljoen et al. (2005), with myrcenone (36–62%), carvone (61–73%), piperitenone (32–48%), ipsenone (42–61%) and linalool (>65%), identified as the major compounds. Philemon et al. (2015) reported a monoterpenoid chemotype with high levels of artemisia ketone and other compounds including *m*-tert-butylphenol, linalool, β-myrcene, tagetone and isopiperitenone. Chagonda et al. (2000) reported three chemotypes from Zimbabwe with high levels of myrcene, linalool and limonene. In a further study, Changonda and Chalchat, (2015) identified a myrcenone-rich variety in the western part of Zimbabwe. Research on *L. javanica* from Tanzania revealed the presence of germacrene-D, neral, geranial, camphor, *cis*- and *trans*-ocimene (Mwangi et al., 1992; Ngassapa et al., 2003).



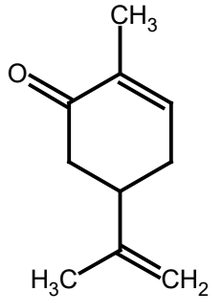
Myrcene



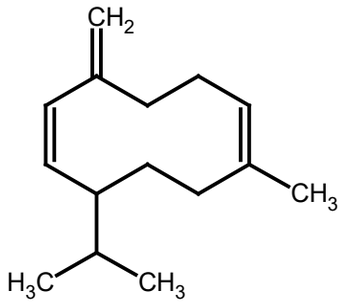
(±)-Limonene



Myrcenone



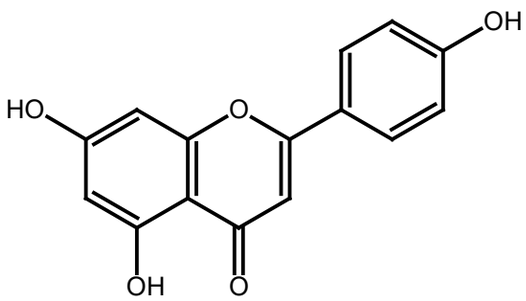
Carvone



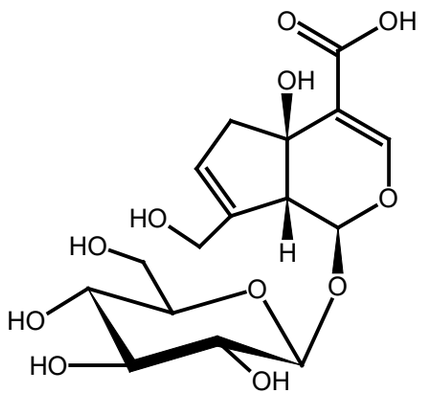
Germacrene-D

Non-volatile constituents

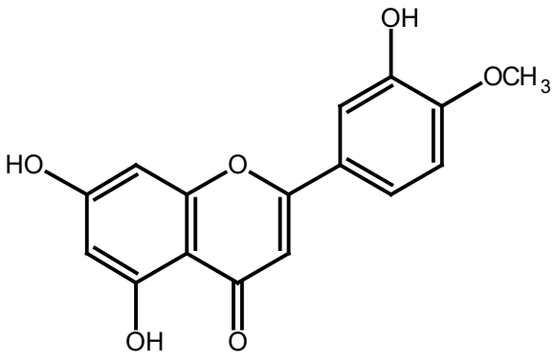
Several classes of non-volatile compounds have been identified in *L. javanica* including organic acids and alcohols (Neidlein et al., 1973), iridoid glycosides (Rimpler et al., 1986), triterpenoids (Buckingham, 2006), flavones (Mujovo et al., 2008), phenolic compounds, caffeic acid derivatives (Olivier et al. 2010), phenolic glycosides, flavonoid alkaloids (Madzimure et al., 2011) and amino acids (Neidlein et al., 1974). Some compounds isolated from the ethanolic extract of the aerial parts include; 4-ethyl-nonacosane, (*E*)-2(3)-tagetenone epoxide, piperitenone, apigenin, cirsimaritin, 6-methoxyluteolin 4′-methyl ether, 6-methoxyluteolin and 3′,4′,7-trimethyl ether (Mujovo et al., 2008). Dlamini (2006) isolated the toxic triterpenoid saponin, icterogenin, and Ludere et al. (2013) isolated lippialactone from the ethyl acetate extract. Rimpler et al. (1986) was the first to report the presence of the iridoid glycosides, theveside and theveridoside currently used as marker molecules for *L. javanica*. Two additional phenylethanoid glycosides, verbascoside and isoverbascoside were isolated and elucidated by Olivier et al. (2010). Other compounds present in the non-volatile fraction include crassifolioside, luteolin, diosmetin, chrysoeriol, tricin, isothymusin, eupatorin, 5-dimethyl noboletin, genkwanin, salvigenin and alkaloid xanthine amino acids (Neidlein et al., 1974).



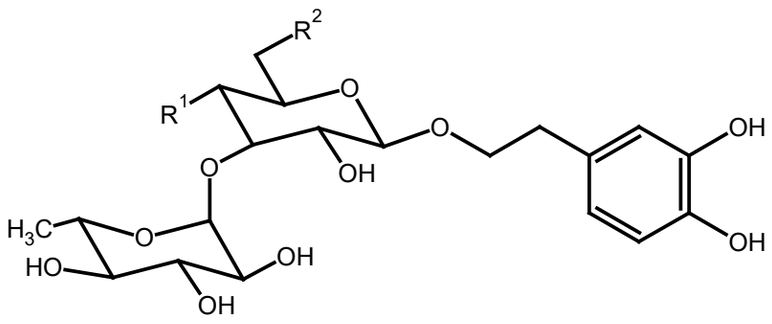
Apigenin

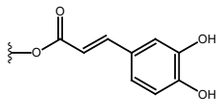


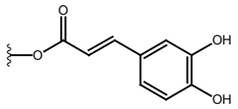
Theveside



Diosmetin



Verbascoside: R^1 =  R^2 = OH

Isoverbascoside: R^1 = OH R^2 = 

Chemical Profiling and Quality Control

HPTLC fingerprint analysis

Plant part: Aerial parts, methanol extract.

Instrumentation: CAMAG HPTLC instrument consisting of an automatic TLC sampler (ATS 4), automatic developing chamber (ADC 2), a Digistore Reprostar 3 (digital imaging device), chromatogram immersion device and TLC plate heater.

HPTLC plates: Silica gel glass plates 60 F254 (Merck).

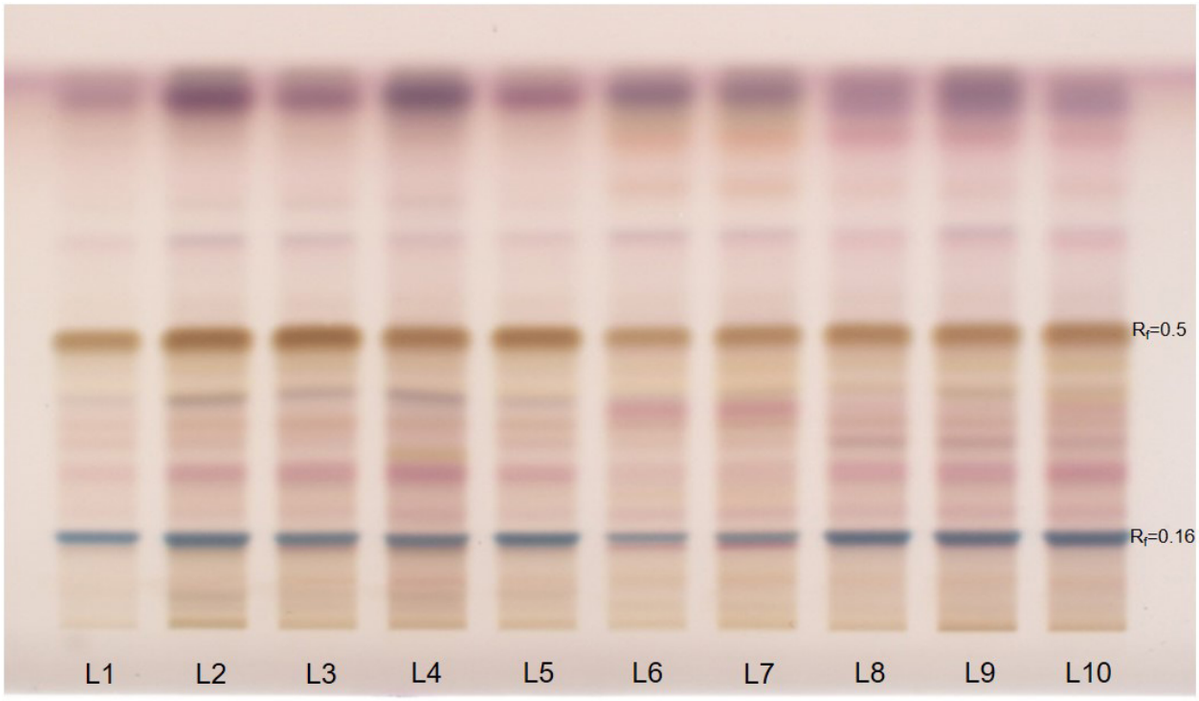
Sample application: Application volume: 10 µL extract (10 mg/mL), spotted as 10 mm bands. Plates developed in a 20 x 10 x 4 cm glass twin-trough chamber to a migration distance of 85 mm. Tank saturation: 20 min at 25 °C and 47% RH, with 25 mL of mobile phase.

Mobile phase: Ethyl acetate:formic acid: acetic acid: water (67:7.4;7.4:8 v/v/v/v).

Derivatisation: *p*-Anisaldehyde prepared by mixing 0.5 g p-anisaldehyde with 85 mL methanol, 10 mL glacial acetic acid and 5 mL sulfuric acid, in that order. The plate was dipped in reagent and heated for 3 min at 100 °C on a TLC plate heater and visualised.

Visualisation: The plate was viewed at white reflectance and transmittance light (RT) using the documentation device (Reprostar 3).

Description of the HPTLC plate: *Lippia javanica* samples from various localities (L1–L10). The samples are characterised by a strong blue band representing theveside (R_f = 0.16) and a brown band for verbascoside (R_f = 0.5).



Plant part: Aerial parts, essential oil.

Instrumentation: CAMAG HPTLC instrument consisting of an automatic TLC sampler (ATS 4), automatic developing chamber (ADC 2), a Digistore Reprostar 3 (digital imaging device), chromatogram immersion device and TLC plate heater.

HPTLC plates: Silica gel glass plates 60 F254 (Merck).

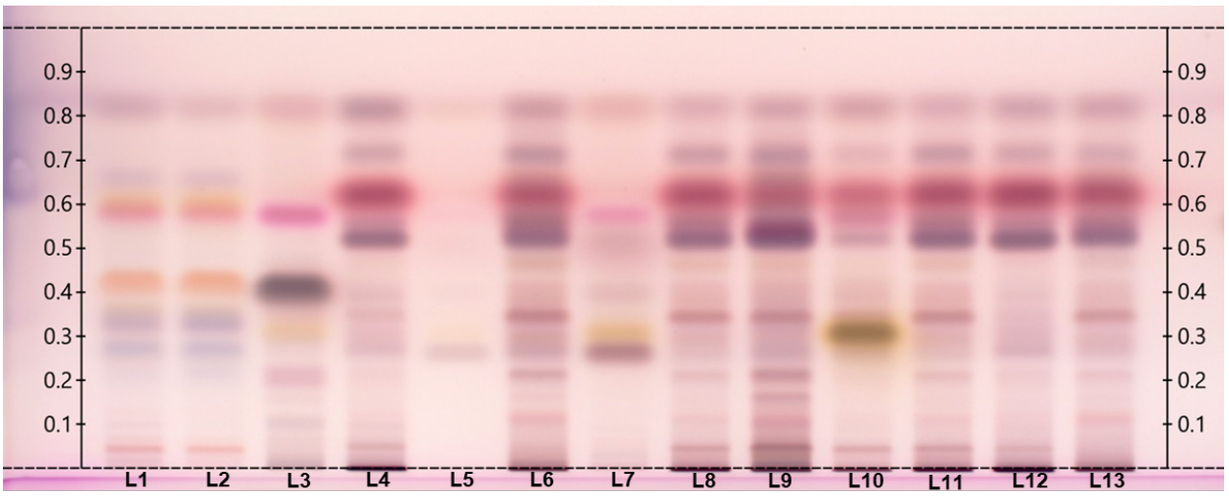
Sample application: Application volume: 2 µL extract (25 µL /mL) and standard (25 µL /mL) spotted as 10 mm bands. Plates developed in a 20 x 10 x 4 cm glass twin-trough chamber to a migration distance of 70 mm. Tank saturation: 20 min at 15 °C and 45% RH, with 25 mL of mobile phase.

Mobile phase: Toluene: ethyl acetate (95:5 v/v).

Derivatisation: The plate was sprayed with 3 mL of *p*-anisaldehyde sulphuric acid. and heated for 3 min at 100 °C on a TLC plate heater and visualised.

Visualisation: The plate was viewed under white reflectance using the CAMAG TLC visualiser 2.

Description of the HPTLC plate: *Lippia javanica* essential oils from various localities (L1–L13) showing variation in the profiles that give rise to the different chemotypes.



Ultra-performance liquid chromatography analysis

Plant part: Aerial parts, methanol extract.

Instrumentation: Waters Acquity Ultra Performance Liquid Chromatographic system with PDA detector combined with Xevo G2QToF mass spectrometer (Waters, USA).

Sample application: Injection volume: 2.0 µL (full-loop injection). Methanol extract concentration: 1 mg/mL.

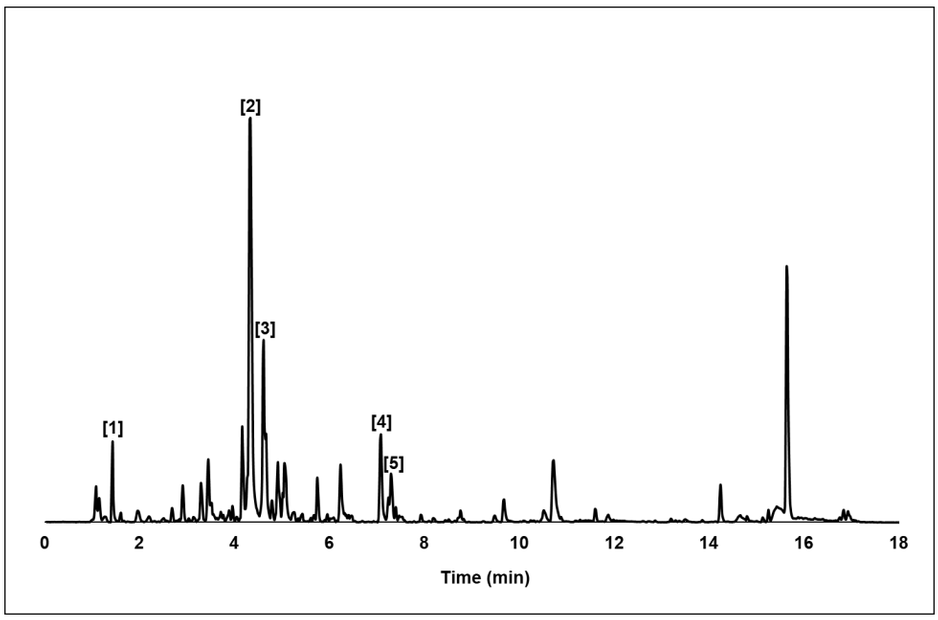
Column: Acquity UPLC BEH C18 column (150 mm × 2.1 mm, i.d., 1.7 µm particle size, Waters)

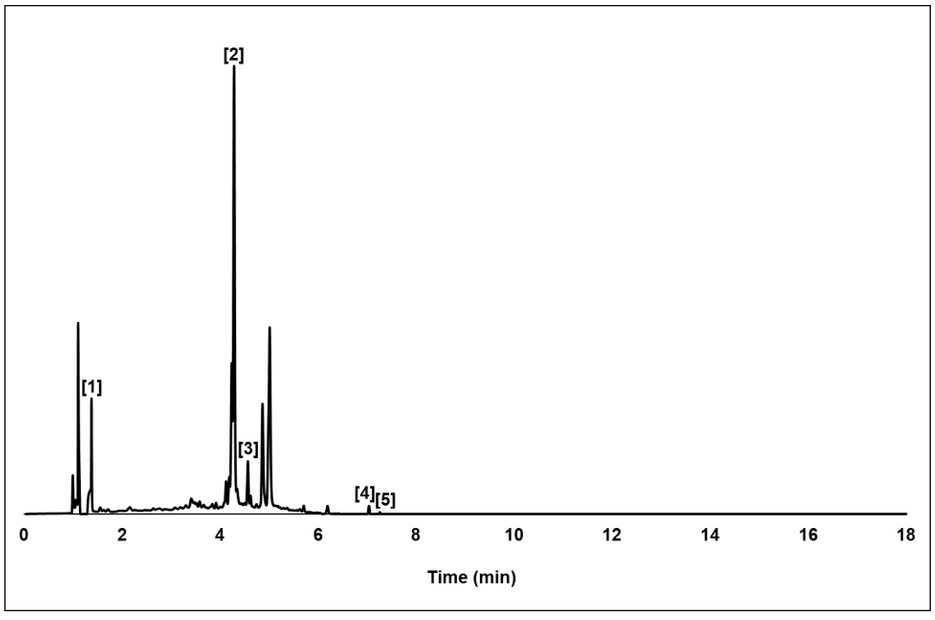
Mobile phase: 0.1% formic acid in water (solvent A) and acetonitrile (solvent B).

Analysis conditions: Gradient elution at a flow rate: 0.3 mL/min, changing as follows: 90% A: 10% B, held for 0.5 min, changed to 40% A: 60% B in 9.5 min, to 100% B in 6 min, held for 1 min and returning to the initial ratio in 1 min, equilibrating the system for 2 min, total run time 20 min.

Mass spectrometry: ESI^-, N^2 used as the desolvation gas. Desolvation temperature 350 °C at a flow rate of 500 L/h, source temperature 100 °C. Capillary and cone voltages, 2500 and 45 V, respectively. Data collected between *m/z* 100 and 1500.

Description of the chromatogram: Chromatograms of *Lippia javanica* methanol extracts obtained by UPLC-ToF-MS ES^- (upper) and UPLC-PDA (lower): [1] = theveside *m/z* = 389.1160, [2] = verbascoside *m/z* = 623.2047, [3] = isoverbascoside *m/z* = 623.2047), [4] = apigenin *m/z* = 269.0265), [5] = diosmetin *m/z* = 299.0386.





Gas chromatography analysis

Plant part: Aerial parts, essential oil.

Instrumentation: An Agilent 6860N chromatograph (Agilent Technologies, Hanova, USA) fitted with a flame ionisation detector and a mass spectrometer.

Sample application: Injection volume 1 µL (split). Essential oil concentration: 20% (v/v) in hexane.

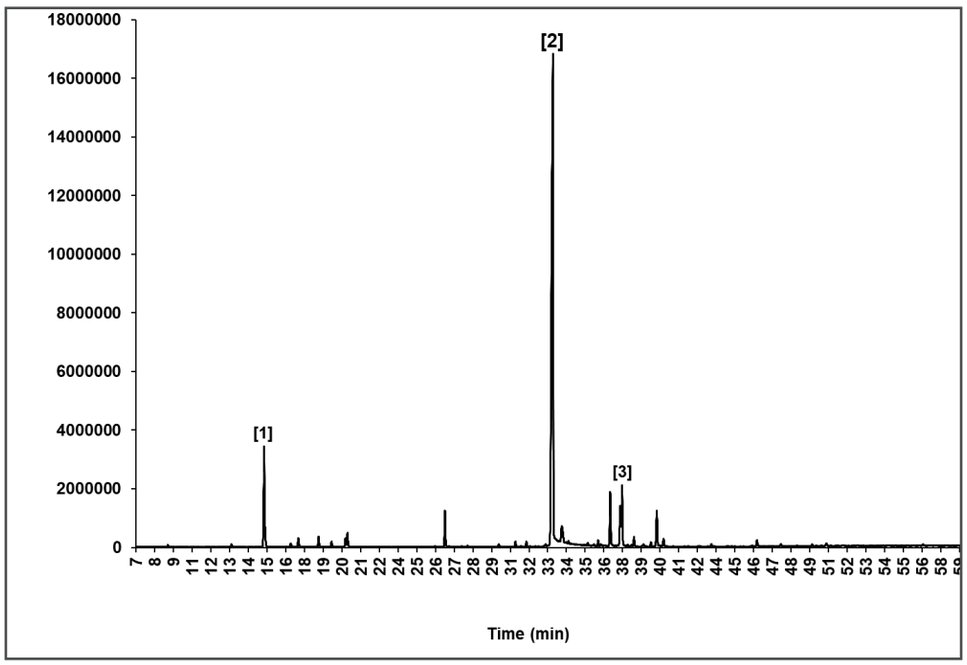
Column: HP-Innowax, 60 m × 250 µm × 0.25 µm (polyethylene glycol column, Agilent Technologies, Hanova, USA).

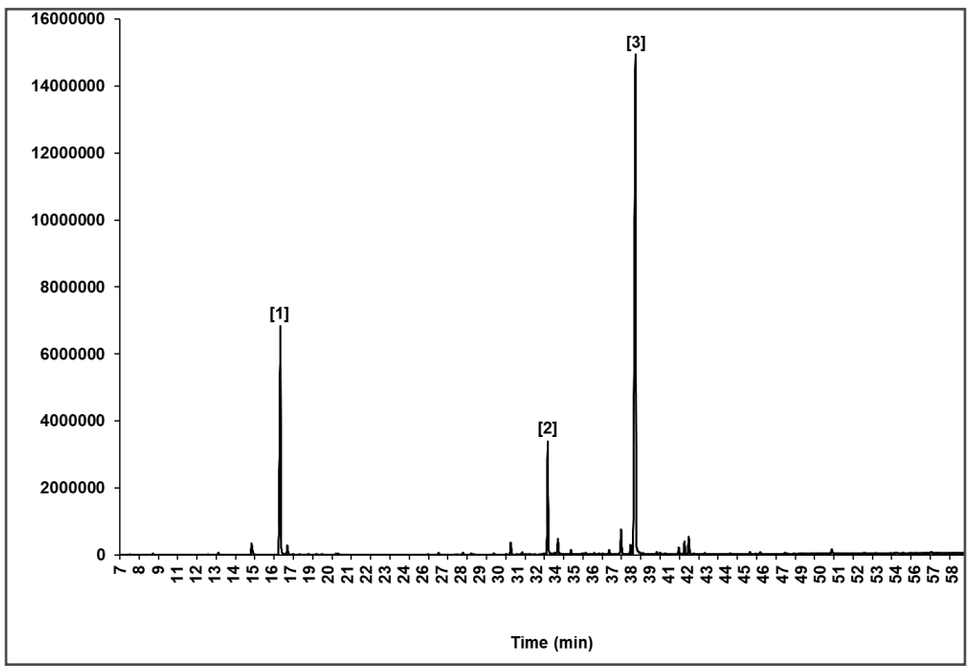
Analysis conditions: Helium carrier gas, Flow rate: 1.2 mL/min, Pressure: 24.79 psi, split ratio: 1:200. Starting oven temperature at 60 °C and then rise to 220 °C at 4 °C/min, holding for 10 min and then up to 240 °C at 1 °C/min. Inlet temperature 250 °C .

Mass spectrometry conditions:
Chromatograms obtained on electron impact at 70 eV on an Agilent 5973 mass selective detector, scanning range: 35 to 550 *m/z* (Agilent Technologies, Hanova, USA).

Identification: Authentic standards, NIST®, Mass Finder®

Description of chromatogram: Total ion chromatograms (TIC) of *Lippia javanica* essential oils indicating major compounds; Top (myrcenone rich chemotype) [1] = myrcene (R_t 15.11, *m/z* 136.1252), [2] = myrcenone (R_t 33.27, *m/z* 150.1044), [3] = germacrene D (R_t 37.64, *m/z* 204.1878) and bottom (carvone rich chemotype) [1] = limonene (R_t 16.85, *m/z* 136.1252), [2] = myrcenone (R_t 33.27, *m/z* 150.1044), [3] = carvone (R_t 38.48, *m/z* 150.44).





Mid-infrared (MIR) spectroscopy analysis

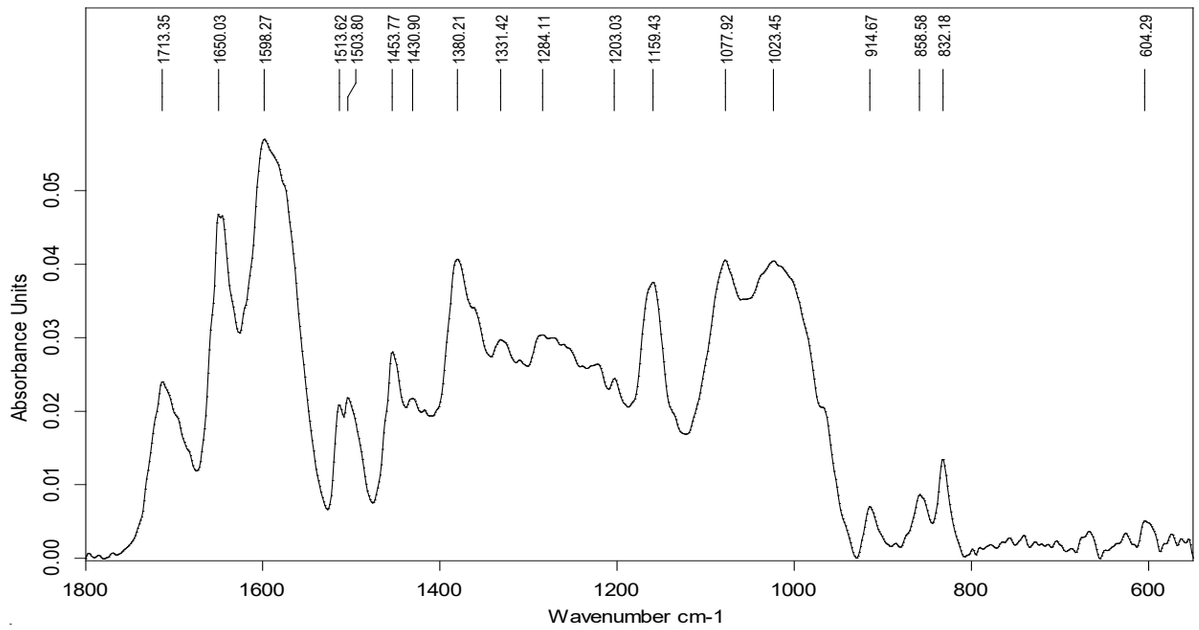
Plant part: Aerial parts, powder.

Instrumentation: Alpha-P Bruker spectrometer, mounted with an attenuated total reflectance (ATR) diamond crystal.

Sample preparation: Aerial parts were powdered and sieved (<500 µm). Powder placed directly onto surface of diamond crystal.

Spectral acquisition: Spectrum was obtained in absorbance mode, with a spectral resolution of 4 cm^{-1} over the range 4000–550 cm^{-1} and captured using OPUS 6.5 software.

Description of spectrum: Mid-infrared spectrum of *Lippa javanica* powder displaying the fingerprint region (1800–550 cm^{-1}).



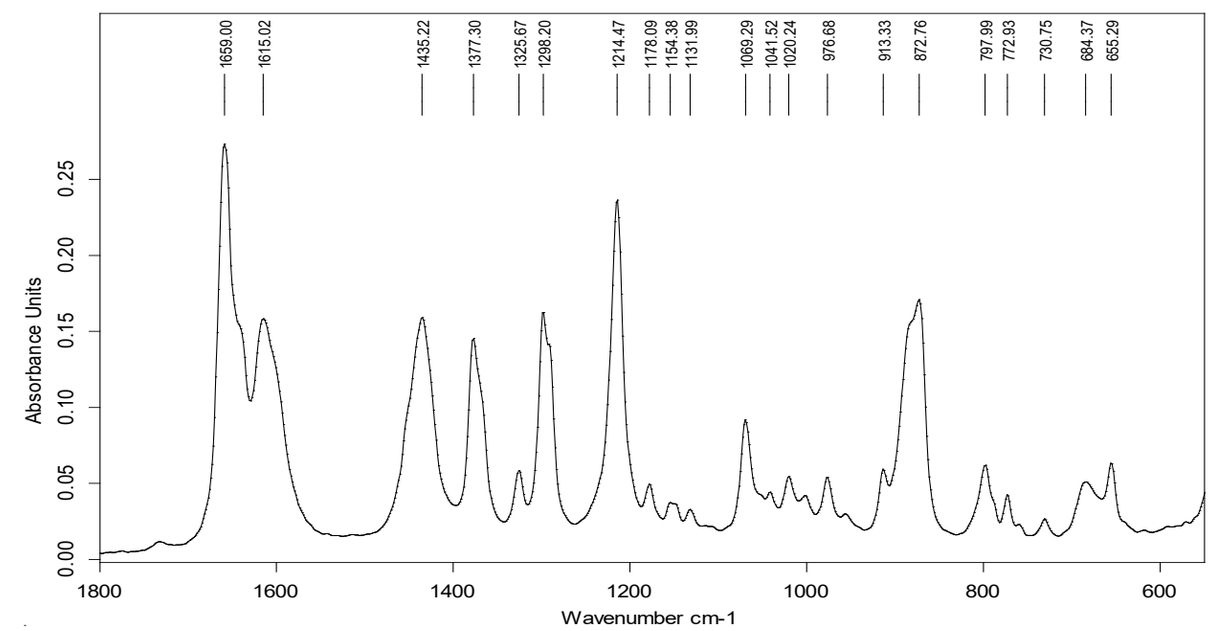
Plant part: Aerial parts, essential oil.

Instrumentation: Alpha-P Bruker spectrometer, mounted with an attenuated total reflectance (ATR) diamond crystal.

Sample preparation: Isolation of essential oil by hydrodistillation of aerial parts. Oil placed directly onto surface of the diamond crystal.

Spectral acquisition: Spectrum was obtained in absorbance mode, with a spectral resolution of 4 cm^{-1} over the range 4000–550 cm^{-1} and captured using OPUS 6.5 software.

Description of spectrum: Mid-infrared spectrum of *Lippia javanica* essential oil displaying the fingerprint region (1800–550 cm^{-1}).



Ethnopharmacology

Lippia javanica has a long history of traditional use in Africa with medicinal applications in treating a wide range of conditions, including pain, fever, infections, inflammation, coughs, colds, bronchitis, influenza, stomach problems, measles, malaria and headaches (Watt and Breyer-Brandwijk, 1962; Hutchings, 1996, 2003; Hutchings et al., 1994; Pascual et al., 2001; Manenzhe et al., 2004). The aerial parts prepared in the form of decoctions are usually used for medicinal purposes, but the roots are also indicated for some conditions. Leaves are crushed and mixed with cold or hot water and the infusion is administered to combat diarrhoea in northern Maputaland, KwaZulu-Natal (De Wet et al., 2010). The Vhavenda people use leaf infusions as anthelmintics, for respiratory and febrile ailments and as prophylactics against dysentery, diarrhoea and malaria (Mabogo, 1990). The plant species was reported as the most frequently used species (91.7%) in a study by Mavundza et al. (2011) to traditionally repel mosquitoes in the uMkhanyakude district of KwaZulu-Natal. It is also commonly used as a herb and spice in the Nkonkobe Municipality, Eastern Cape Province of South Africa (Asowata-Ayodele et al., 2016). Overall, traditional applications of *L. javanica* are wide ranging and fall into the following eight categories for ease of reference. (i) Respiratory complaints (leaves, stems, twigs and roots) - asthma, blocked nose, bronchitis, chest pains, colds, cough, influenza, lung infections, pneumonia, runny nose, dyspnoea and tuberculosis; (ii) Gastrointestinal diseases (leaves, twigs, roots) - amoebiasis, anthelmintics, diarrhoea, gangrenous rectitis, prophylactic against diarrhoea and vomiting, ulcers and abdominal pains; (iii) Malaria (leaves, stems, twigs, roots and whole plant) - fever, prophylactic against malaria and mosquito repellent; (iv) Skin conditions (leaves, roots, twigs) - acne, boils, chicken pox, febrile rashes, inflammation, pubic sores, scabies, shingles, heat rash, scratches, stings, bites, sores, measles and wounds; (v) Pain (leaves) - earache, backache, headache and migraines, sore eyes, sprained joints, sore throat, and tonsillitis; (vi) Ethnoveterinary uses (whole plant, leaves, twigs, stems) - disinfecting suspected anthrax-infested meat, getting rid of ticks and other ectoparasites and insect repellent; (vii) Other conditions (leaves, stems, twigs, roots) - antidote, anaemia in pregnancy, cancer, diabetes, convulsions, fatigue, HIV symptoms, kidney problems, night blindness, pre intra-, and post-partum complications, venereal diseases, weak joints, air freshener, psychotropic behaviour, removing bad luck and sleeplessness, driving away bad spirits, and protection against dogs and lightning; (ix) Culinary uses (leaves, stems, twigs) - herbal caffeine-free tea and general health tonic (Maroyi et al., 2017).

Commercialisation

Due to its aromatic nature, *L. javanica* is a popular garden plant that serves to repel insects, and as household fragrance. Commercial cultivation is done mainly for essential oil production. The oil is an important ingredient in the fragrance industry. The repellence properties of the essential oil have contributed to the successful commercialisation of the plant in South Africa. A mosquito/insect repellent formulated into candles with higher potency compared to other insect repellents is branded and marketed locally under Ulwazi Botanicals (Maharaj et al., 1995). Wild-harvested leaves of *L. javanica* have been used since the mid-1990s in branded infusions (herbal teas) to treat bronchitis, colds, coughs and fever (Van Wyk, 2011). An infusion of the aerial parts is popularly marketed and consumed as herbal tea for its health benefits. 'Mosukudu' and 'Zimbani', as the tea is branded and sold in Botswana, South Africa and Zimbabwe, is popular in Africa and expected to expand to international markets. There is an increase in the demand for *L. javanica* herbal tea in the light of growing health consciousness worldwide, with the potential demand for the species and its products estimated at 100 ton per year on the local market and 1000 ton per year on the export market.

In vitro Studies

Studies on *L. javanica* indicated a wide range of *in vitro* pharmacological activities that include anticancer, antimalarial, antimicrobial, anti-oxidant, antiplasmodial, mosquito repellence, pesticidal and various other effects. Fouche et al. (2008) reported the anticancer effects of a dichloromethane root extract of *L. javanica* against three human cancer cell-lines, exhibiting TGI values of 1.82 µg/mL, 1.86 µg/mL, 2.09 µg/mL for MDA-MB-435 (breast), MDA-N (breast) and MALME-3M (melanoma), respectively. A few isolated compounds, including linalool, limonene and α-pinene have also been reported to exhibit antitumor activities (Fouche et al., 2008; Yang et al., 2001). Govere et al. (2000) demonstrated the insect repellence activity of *L. javanica* where topical application of the alcohol extract exhibited 76.7% protection against *Anopheles arabiensis* mosquitoes for a period of 4 hours. Lukwa et al. (2009) also reported that topical application of 5 mg/cm^2 *L. javanica* led to 100% protection against *Anopheles aegypti* for 8 hours. Ethanol extracts of the leaves of *L. javanica* exhibited larvicidal activity (21%) against *A. arabiensis* mosquitoes (Mavundza et al., 2013). Mavundza et al. (2014) reported that the dichloromethane and ethanol leaf extracts of *L. javanica* displayed adulticidal activity against *A. arabiensis*, with activities of 45% and 55% mortality, respectively. Extracts of *L. javanica* were also effective in killing larvae (LC_{50} = 125.34 mg x 10(3) µg/mL) of the *A. gambiae* mosquitoes (Lukwa, 1994). In line with the use of *L. javanica* for malaria, the oil demonstrated activity against *Plasmodium falciparum* with an IC_{50} value of 8 µg/mL (Manenzhe et al., 2004). It was demonstrated by Oketch-Rabah et al. (1999) that the lipophilic compounds in the nonpolar extract (CH_2CH_2:EtOAc, 1:1) exhibited antiplasmodial activity. The methanol extract of *L. javanica* has also been reported to exhibit antiplasmodial activity using the parasite lactase dehydrogenase (pLDH) assay (Clarkson et al., 2004; Ayuko et al., 2009). Prozesky et al. (2001) reported an IC_{50} value of 4.26 µg/mL for the leaf acetone extract against a chloroquine resistant strain of *P. falciparum*. The antimicrobial activity of *L. javanica* essential oil was reported against three strains of *Staphylococcus aureus* (inclucing methicillin-resistant strains), two strains of *Candida albicans*, and one strain of *Cryptococcus neoformans*. All isolates were inhibited by ≤ 1% of the oil (Huffman et al., 2002; Osée et al., 2004). Samie et al. (2009) reported that the extracts of *L. javanica* demonstrated good antibacterial activity with a minimum inhibitory concentration (MIC) of 90 µg/mL. *In vitro* antimicrobial activity of the essential oil has been reported against respiratory pathogens such as *Klebsiella pneumoniae, C. neoformans* and *Bacillus cereus* (Viljoen et al., 2005). Various solvent extracts including methanol, acetone, hexane and dichloromethane, were tested and proven to exhibit good antimicrobial activity against *S. aureus, Enterococcus faecalis, Escherichia coli* and *Pseudomonas aeruginosa* (Shikanga et al., 2010; Lekganyane et al., 2012; Samie et al., 2005). When tested against *S. aureus* and *E. coli*, the oil displayed moderate activity at a concentration of 10 mg/mL (Manenzhe et al., 2004). Samie et al. (2009) demonstrated that the compound, piperitenone, isolated from *L. javanica* exhibited antibacterial activity against *Acinetobacter calcoaceticus, Micrococcus kristinae, Salmonella typhi* and *S. aureus*, with MIC values ranging between 12–50 µg/mL. The antimicrobial activity of crude extracts of *L. javanica* was investigated against 31 *Helicobacter pylori* strains. The strains were inhibited by all the extracts with marked susceptibility of strains (100%) for the acetone extract, followed by the methanol extract (60%). The MIC values ranged from 0.00195–1.25 mg/mL for the acetone and methanol extracts, respectively (Nkomo et al., 2011). Methanol and water extracts of *L. javanica* were investigated for the ability to control a microbial trigger for ankylosing spondylitis *(K. pneumoniae*) and were found to be effective inhibitors (Cock et al., 2014b). The extracts were also effective against *Proteus mirabilis* and *P. vulgaris* (Cock et al., 2014a). The essential oil and fractions were assessed for antimicrobial activy against two bacterial strains

(*B. cereus* and *K. pneumoniae*) and one fungal pathogen (*C. neoformans*). *K. pneumoniae* was found to be the most susceptible bacteria (MIC < 5 mg/mL) (Endris et al., 2016). Extracts of *L. javanica* were inhibitory against fungal growth in clinical isolates of *Candida albicans*, *C. krusei* and *C. neoformans* (Samie et al., 2010). *Fusarium* species and other fungal pathogens have also demonstrated susceptibility to *L. javanica* extracts (Shikanga et al., 2010; Thembo et al., 2010). Organic extracts and the essential oil of *L. javanica* were also tested against resistant bacterial strains (*E. faecalis, S. aureus, B. cereus, K. pneumoniae, Acinetobacter baumannii, P. aeruginosa, E. coli and Serratia marcescens*). The organic extracts, followed by the essential oils, were more effective against the resistant strains than the antibiotic (ciprofloxacin) (Van Vuuren et al., 2017). Shikanga et al. (2010) evaluated the relationship between phenolic compounds and the antioxidant activities of tea infusions prepared from *L. javanica* using the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) method. *Lippia javanica* compared well to the popular black, green and herbal tea brands with an EC_{50} of 358 µg/mL and contained a high phenolic content of 14.8 mg/mL of dry weight gallic acid equivalent (Shikanga et al., 2010; Katerere et al., 2012). In other studies, *L. javanica* exhibited anti-oxidant activity in the DPPH assay (Narzary et al., 2016) with an IC_{50} value of 135.0±1.49 µg/mL, while Swargiary et al. (2016) reported an anti-oxidant activity of (48.57±3.07 µg AAE/milligram extract) for the extract. *Lippia javanica* has high radical scavenging activity (83.77±0.8%), which is probably due to a high total phenolic content (Maroyi, 2017). Endris et al. (2016) assessed the anti-oxidant property of the essential oil using the free radical scavenging assay and obtained an IC_{50} value of 16.6 µL/mL. Extracts of *L. javanica* exhibited significant dose dependent repellence response in adults of *Hyalomma marginatum rufipes* with 107 mg/mL of extract causing 100% repellence at 30 min and 1 h (Magano et al., 2011). In another study, *L. javanica* aqueous leaf extract at 10% and 20% (w/v) was effective at controlling cattle ticks (Madzimure et al., 2011). Peripheral blood samples collected during the study showed no haemoparasites in treated cattle, implying that animals did not suffer from tick-borne diseases. McGaw et al. (2000) screened *L. javanica* for anthelmintic activity using the free-living nematode, *Caenorhabditis elegans*. The crude ethanol and hexane extracts were active at 2 mg/mL, with the 7-day incubation assay. The two extracts also exhibited good anthelmintic activity against *Paramphistomum* species at 50 mg/mL concentration and the time taken for paralysis and death was recorded as 0:56±0:09 h and 1:35±0:07 h, respectively (Swargiary et al., 2016). Interactions of *Cucumis myriocarpus, L. javanica* and *Ricinus communis* on suppression of the nematode, *Meloidogyne incognita* and improving tomato (*Lycopersicon esculentum)* productivity were reported. The extracts successfully reduced nematode infection and improved fruit yield, dry shoot weight, and plant height (Mashela et al., 2007). Extracts of *L. javanica* have also demonstrated promising *in vitro* inhibition of 15-lipoxygenase (97.4% at 25 µg/mL), nitric oxide production (97% at 25 µg/mL), moderate anti-oxidant and low acetylcholinesterase activity (Dzoyem et al., 2015). (*E*)-2(3)-tagetenone epoxide and piperitenone have been reported to exhibit antiviral activity against HIV-1 reverse transcriptase strain by 91 and 53%, respectively, at 100 µg/mL (Mujovo et al. 2008). The antimycobacterial activity of organic extracts of *L. javanica* was evaluated. The acetone extract displayed activity against *Mycobacterium smegmatis* with an MIC of 0.47 mg/mL (Masoko et al., 2013). Other researchers (York et al. 2011; Masoko et al., 2013) have also documented the antimycobacterial activity of *L. javanica* extracts against *M. smegmatis*.

In vivo Studies and Clinical Trials

Lippia javanica was reported to exhibit antidiabetic effects in white albino diabetic mice. Following oral and intraperitoneal administration of the aqueous extract, the blood glucose levels in the mice were significantly lowered (Arika et al., 2015). Field trials conducted on 'Valencia' oranges showed that polar extracts of *L. javanica* and *L. rehmannii* caused significant inhibition of mycelial growth (*Penicillium digitatum*) at concentrations above 0.6 mg/mL (Shikanga et al., 2009). The observed activity was largely ascribed to the presence of verbascoside in the plant extracts. The extract of *L. javanica* was investigated for pesticidal activity and effectively controlled key pest species on common bean plants (*Phaseolus vulgaris*) under field conditions (Mkenda et al., 2015). In another study, the inclusion of *L. javanica* in quail diets at 25 g/kg feed, promoted similar growth performance, health status and meat quality traits as the commercial grower diet containing antibiotics (Mnisi et al., 2011). *Lippia javanica* leaf meal (5 g/kg feed) was evaluated for growth performance, carcass characteristics and fatty acid profiles over a 42-day feeding period in broiler chicks' diets. The broilers fed *L. javanica* had significantly lower feed intake compared to the negative and positive control groups, but higher average daily weight gain, lower feed conversion ratio and higher slaughter weights. Overall, the findings from the study showed that inclusion of *L. javanica* in broiler diets at 5 g/kg feed had positive influences on growth performance, carcass characteristics and fatty acid profiles of broiler meat (Mpofu et al., 2016). To date, there are no documented clinical trials on *L. javanica* extracts or products.

Safety

Lippia javanica is consumed as herbal tea with no adverse reactions reported to date. While anecdotal evidence suggests that *L. javanica* has low mammalian toxicity, scientific studies have not documented evidence of toxicity. Arika et al. (2016) reported alterations in biochemical and hematological parameters following chronic and sub-chronic administration of *L. javanica* extracts to mice. Substantial changes in body and organ weight were observed after a dose of 450 mg/kg to 1000 mg/kg was given to mice. These reports suggested potential toxicity when consumed in high doses, thus caution should be taken when using the herb. In another study, Madzimure et al. (2011) reported that all mice within 48 h fed with *L. javanica* leaf aqueous extract at 12.5–37.5% v/v were lethargic and the overall mortality was 37.5%. Photosensitisation effects and liver damage in livestock due to the presence of icterogenic compounds in *L. javanica* have been documents (Van Wyk et al., 2009). The essential oil of *L. javanica* was reported to exhibit moderate toxicity towards *Artemia salina* (LC_{50} value of 129.11 µg/mL) (Adeogun et al., 2018). The oil also showed fumigant toxicity against adult *Sitophilus zeamais*, with increased dose. The LD_{50} fumigant toxicity values at 72 and 120 h were 254 and 216 µg/cm^3 air, respectively (Kamanula et al., 2017). The oil also showed contact toxicity against adult *S. zeamais* with an LC_{50} value of 6.22 mg/mL.

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Disclaimer

The content presented in this monograph represents a succinct collation of scientific and ethnobotanical literature. Those seeking to utilise botanicals for healthcare should do so only under the guidance of a qualified healthcare professional.

Contact Information:

Professor Alvaro VILJOEN

DST-NRF Chair in Phytomedicine

Director: SAMRC Herbal Drugs Research Unit

Department of Pharmaceutical Sciences

Tshwane University of Technology

Private Bag X680

Pretoria | 0001

SOUTH AFRICA

Tel +27 12 382 6360 | Fax +27 12 382 6243

www.alvaroviljoen.com | viljoenam@tut.ac.za