



Received on 05 April 2016; received in revised form, 19 May 2016; accepted, 26 May 2016; published 31 May 2016

PHYTOCHEMISTRY AND ETHNOPHARMACOLOGY OF *LIPPIA* GENUS WITH A STATEMENT ON CHEMOTAXONOMY AND ESSENTIAL OIL CHEMOTYPES

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Keywords:

Lippia, Phytochemistry, Essential oils, Classification, Chemotypes, Chemotaxonomy

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ABSTRACT: *Lippia* is a genus of flowering plants belonging to the Verbenaceae family. It contains about 220 species with diverse ethnopharmacological applications. Myriad of biologically active phytoconstituents abound in *Lippia*. The essential oil chemotypes found in *Lippia* species included myrcenone rich-type, carvone rich-type, piperitenone rich-type, ipsenone rich-type, linalool rich-type, citral rich-type, carvacrol rich-type, thymol rich-type and lippiol rich-type. Other constituents apart from essential oils isolated and chemically characterized were highlighted. β -caryophyllene and iridoid glycosides were notable as chemotaxonomic marker compounds which were common to many of *Lippia* species.

INTRODUCTION: Chemotaxonomy refers to the investigation of the distribution of groups of biosynthetically related chemical compounds in a series of related or supposedly related plants¹. It can also be loosely defined as the identification and classification of organisms by comparative analysis of their biochemical composition. A wealth of information can be sorted out by placing plant genera in the chemotaxonomic context. Chemotype is generally defined as a distinct population within the same species (plant or microorganism) that produces different chemical profiles for a particular class of secondary metabolites².

Lippia is one of 41 genera of flowering plants belonging to the family Verbenaceae³. It contains roughly 220 species of tropical shrubs, herbs, and trees that are widely distributed around the world⁴. Some of these species include *adonensis* (kere), *multiflora* (bush tea), *lugosa*, *organoides*, *graveolens*, *chevalieri*, *alba*, *javanica*⁵, *sidiodes*, *gracilis*, *citriodora*⁶, among others. Below are herbarium samples of *Lippia chevalieri* **Fig. 1** and *Lippia multiflora* **Fig. 2**.

In this review, essential oils and non-essential oil constituents were investigated toward identification of essential oil chemotypes and chemotaxonomic markers in the *Lippia* genus. Essential oils showed great abundance and overwhelming chemical diversity in *Lippia*.

Chemotypes from other classes of secondary metabolites have not been extensively isolated, studied and documented when compared to the

	<p>QUICK RESPONSE CODE</p>
	<p>DOI: 10.13040/IJPSR.0975-8232.IJP.3(5).201-11</p>
<p>Article can be accessed online on: www.ijpjournal.com</p>	
<p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.3(5).201-11</p>	

essential oils. By and large, this review seeks to classify various species of *Lippia* into chemical

groups, using essential oils to show chemotypic variation.



FIG. 1: *LIPPIA CHEVALIERI*



FIG. 2: *LIPPIA MULTIFLORA*

Ethnopharmacology: Plants belonging to the *Lippia* genus have been widely used in ethnobotany throughout South and Central America and in tropical Africa as foods, medicines, sweeteners and in beverage flavoring⁷. The *Lippia* species have a long history of use in traditional medicinal applications some of which have been scientifically validated. They are mostly used in the treatment of respiratory and gastrointestinal disorders. Additionally, they exhibit anti-malarial, spasmolytic, sedative, hypotensive and anti-inflammatory activities^{8, 9, 10}. The essential oils of *L. alba* had been reported to possess anti-spasmodic, digestive, anti-hemorrhoidal and anti-asthmatic activities¹¹. Also, antifungal, antibacterial, antiviral, anti-inflammatory and cytotoxic activities have been reported for *L. alba*^{12, 13, 14, 15, 16}.

The cytotoxic and antitumor effects of *L. alba* extracts and some significant components of its essential oils, such as limonene and citral, have been demonstrated in HL-60 human promyelocytic leukemia cells, K562 human erythroleukemic cells, HepG2 human hepatocellular liver carcinoma cells and HeLa human cervix epithelioid carcinoma cells^{17, 18, 19}. *L. gracilis* also exhibits antitumor activity²⁰. *L. multiflora* leaves and inflorescence are widely used as spices in cooking and traditional medicine.

The leaf is used as a vegetable, and the flower with seed are used for soup. It has been used in many ethnopharmacological applications to ameliorate bronchial inflammation, malaria fever, conjunctivitis, gastrointestinal disturbance, enteritis, coughs and colds²¹. *L. multiflora* possesses hypotensive, fatigue relieving, and diuretic properties²².

It has also been used as a substitute for tea and as a mouth disinfectant²³. Analgesic and antipyretic activities have also been documented for *L. multiflora*. *Lippia adoensis* extracts were used medicinally by a variety of indigenous people for treatment of skin infection²⁴. *Lippia* species are also useful in culinary seasoning and as insect repellants; *L. dulcis* has demonstrated anti-proliferative activity *in vitro* in different cancer cells²⁵. Virucidal activity has also been demonstrated *L. dulcis*²⁶. It was recently reported that three compounds from *L. javanica* were able to inhibit the HIV-1 reverse transcriptase enzyme²⁷. The table below comprehensively captures the ethnopharmacological applications of *Lippia* species **Table 1**. Meanwhile, the medicinal effects of *L. multiflora* have been attributed to essential oils, glycosides and other phytochemical components²⁸.

TABLE 1: TRADITIONAL USES AND PHARMACOLOGICAL ACTIVITIES OF *LIPPIA* SPECIES

Species	Traditional uses	Pharmacology	References
<i>L. affinis sidoides</i> Cham. ; <i>L. alba</i> (Mill.) N. E. Brown	A, B, C, D, E, G, H, K, Q, R, S	O A, B, D, M, N, T, V	29 30, 31, 32, 33 34, 35, 36, 38
<i>L. geminata</i> H. B. K	A, B, D, G, K, Q, S	A	33, 37, 38

<i>L. aristata</i> Schau.		O	29
<i>L. chevalieri</i> Moldenke	B, P, R, S	P	38
<i>L. citrodora</i> (Ort) HBK	A, B, C, G, I, Q	A, B, Y	39, 40, 41, 42
<i>L. dulcis</i> Trevir	A, C, D, G, I, K, R, W	C, M	30, 43, 44, 45, 46
<i>L. formosa</i> T. S Brandgee		M	47
<i>L. gracilis</i> HBK	E	M	48
<i>L. grandifolia</i> Hochst.		L, M	59
<i>L. grata</i> Shau		Q	50
<i>L. graveolens</i> HBK	A, C, D, K, Q, R, U, W		30, 47, 51
<i>L. javanica</i> (N.L Burm) Spreng.	A, Q, R	L, M	52, 43
<i>L. micromera</i> Shau	C, G, I, R		30
<i>L. multiflora</i> Moldenke	H, J, P, R	F, J, N, P	53, 39, 28, 54, 9
<i>L. nodiflora</i> (L.) Michx	A, I, K, M, P, R, Q, M, S	M	55, 38
<i>L. organoides</i> H.B.K	C, G, R		30
<i>L. palmeri</i> S. Wats		F, M	49
<i>L. reptans</i> H.B.K	D, G		56
<i>L. sidoides</i> Cham		B, F, J, M, Q, Z	57, 52, 50
<i>L. somalensis</i> Vatke		L	51
<i>L. turbinata</i> Griseb	G		58
<i>L. ukambensis</i> Vatke		L, M	51

A: Analgesic/anti-inflammatory/antipyretic; B: Sedative; C: Culinary seasoning; D: Remedy for diarrhea and dysentery; E: Cutaneous diseases treatment; F: Antifungal; G: Remedy for gastrointestinal disorders; H: Remedy for hepatic/cholorectic/vesicle disorders; I: Diuretic; J: Antihypertensive; K: Menstrual disorders remedy; L: Larvicidal/repellent; M: Antimicrobial; N: Antiviral; O: Molluscicidal; P: Antimalarial; Q: Antispasmodic; R: Respiratory diseases treatment; S: Treatment of syphilis and gonorrhea; T: Cytostatic; U: Antidiabetic; V: Anticonvulsant; W: Abortifacient; X: Stimulant; Y: Pro-convulsant; Z: Local anesthetic.

Phytochemistry: The genus *Lippia* consists of nearly 220 species of herbs, shrubs and small trees which are often aromatic. Of these, thirty-nine species have had some previous work done on their essential oil compositions. Some species of *Lippia* are composed of a wide variety of chemically variable, volatile compounds that present biological properties^{21, 59, 60}. The phytoconstituent which was found to occur in the highest frequency in *Lippia* essential oils was limonene. Other components found in these oils, in order of decreasing frequency, were: p-cymene, α -pinene, camphor, β -caryophyllene, linalool, thymol and carvacrol⁶¹. Essential oils are aromatic, or odoriferous, oily liquids, sometimes semi-liquid or solid, obtained from plant material, for example, flowers, buds, seeds, leaves, twigs, bark, herbs, woods, fruits, and roots. Depending on the kind of oils and the quality, essential oils can be used in different industries.

Essential oils are applied in the food industry as a flavoring, the perfume industry for fragrances, and the pharmaceutical industry for adding taste or smell or suppressing the less desirable medicated flavor. The use of essential oils in health care are called 'aromatherapy.' The knowledge of chemical constituents of essential oils is of fundamental importance to the pharmaceutical, food, and

perfumery industries. As the use of aromatic compounds requires detailed chemical characterization and evaluation of possible modifications within their compositions, which are due to the different geographical origins and climatic conditions and different population genetics that can lead to the formation of different chemotypes^{62, 63, 64}.

Phytochemical studies by several researchers have shown the presence of essential or volatile oil in the aerial part of *L. Multiflora*, which has been extracted and characterized by some workers using instrumental methods like hydro-distillation and Gas Chromatography-Mass Spectrometry (GC-MS). Analysis of the oil by GC-MS revealed, among others, the presence of terpineol, α - and β -pinene which are known to be lethal to lice⁶⁵. Others have also used traditional classical methods of maceration in organic solvents to isolate the oil or components of the oil and then characterize by using GC-MS and other spectrometric methods like Nuclear Magnetic Resonance (NMR) and Infra-Red spectrometry^{66, 10}.

Investigators have widely studied the oil which is believed traditionally to possess some pharmacotherapeutic activities in the field. The chemical composition has necessitated the

classification of the oil into different chemotypes to guide its identification and application⁶⁷. Some chemotypes could be seen along the monoterpenoid (rich in thymol and its derivatives, *p-cymene*, and carvacrol) and sesquiterpenoid (rich in ipsdienone and ocimene isomers)⁶⁸. Another classification placed the analyzed samples into five chemotypes namely, linalool (29%) and germacrene D (28%) rich oil, 1,8-cineole (43-47%) and sabinene (12-15%) rich oil, high farnesol (camphoraceous) rich oil, high sesquiterpenes (45-70%) rich oil and high monoterpenes rich oil (*p-cymene* 14-19%, thymol 30-40%, thymol acetate 14-17%)⁶⁹. It is clear that the variation in chemical composition could be due to factors bordering on environmental stress and genetics.

Additionally, GC analysis of extracts *L. alba* revealed most constituents belonging to the terpene class of hydrocarbons: Chemotype 1 (citral, β -myrcene, limonene), Chemotype 2 (citral, limonene), Chemotype 3 (carvone, limonene)⁷⁰. Non-essential oil constituents found in *L. alba* include iridoids and phenylpropanoids in the roots (theveridoside, muscaveroside). Essential oils of *L. javanica* are classified into 5 chemotypes based on the mono and sesquiterpene contents⁷¹. Some iridoid glycosides including theveridoside were isolated from *L. javanica* and were considered as chemotaxonomic markers for the genus *Lippia*⁷².

According to Oliviera and co-workers⁸³, Essential oils from *L. organoides* show a high content of oxygenated monoterpenes (66.0%), monoterpene hydrocarbons (20.7%), sesquiterpene hydrocarbons (9.0%) and oxygenated sesquiterpenes (1.1%). The two major compounds among monoterpenes were carvacrol (38.6%) and thymol (18.5%); among

sesquiterpene hydrocarbon was (E)-caryophyllene (5.9%).

The major constituents of *L. sidoides* are thymol and carvacrol. Other important ones include the oxygenated monoterpene 1,8-cineole, isoborneol and bornyl acetate⁶³. On another note, the main constituents of *L. citriodora* include geranial, neral, and limonene constituting 66.3% of the total essential oil yield in May and increasing to 69% in September^{73, 74, 75, 76}. In the separate study, the essential oil of *Lippia citriodora* revealed cis-sabinene hydrate (38.99%), spathulenol (10.4), cuparene (6.81%), α -terpineol (5.05%), geranyl acetate (3.91%), β -pinene (3.46%) and E citral (3.4%) as the major Compounds identified. Oxygenated monoterpene group was predominant in the essential oil of *Lippia citriodora*⁶. Citral, a mixture of the E- and Z-isomers, was found to be the main constituent of the *L. rehmannii* essential oils, while borneol, camphor, neryl acetate, isocaryophyllene, *p-cymene*, β -caryophyllene, and β -caryophyllene oxide were other major compounds identified⁷⁷. *L. gracilis* essential oils had thymol as a major bioactive component²⁰.

L. graveolens essential oil contained 45 chemical compounds, and the main components were carvacrol, thymol, eugenol, ocimene, pinene, and linalool, among others⁷⁸. On the other hand, essential oil of the leaves of *L. chevalieri* is composed mainly of thymol (27.4%), *p-cymene* (21.1%), and 2-phenyl-ethyl-propionate (12.6%), while the oil from the flower is composed of β -elemene (33%), ethyl cinnamate (30.3%) and α -amorphene (12.4%)⁷⁹. Aromatic volatile oil of *L. microphylla* was rich in monoterpenes, especially cineole, terpineol and thymol⁸⁰.

TABLE 2: OTHER CHEMICAL CONSTITUENTS OF LIPPIA SPECIES

Species	flavonoids	Other compounds	References
<i>L. alba</i> (Mill.) N.E Brown	Flavonoid 4-sulphates	Tannins (low), geniposide (iridoid), triterpenic saponins, resin, mucilage, alkaloids, saponins, sterols	31, 32, 37, 38
<i>L. canescens</i> Kunth	Flavone aglycones, flavones mono- and di-sulphates		81
<i>L. citriodora</i> (Ort.) H.B.K	Salvigenin, eupatorin, eupafolin, hispidulin, 6-hydroxyluteolin, 7-O- β -glucoside, luteolin, cismaritin,	Verbacosides	82, 83

<i>L. dulcis</i> Trevir.	diosmetin, apygenin	Verbacosides, alkaloids	48
<i>L. graveolens</i> H.B.K	Naringenin and pinocembrin	lapachenol	53
<i>L. javanica</i> (N.L Burm.) Spreng.		icterogenin	43
<i>L. multiflora</i> Moldenke	Flavonoids	Verbacoside, isoverbacoside, sterols, carotenoids	54, 55
<i>L. nodiflora</i> (L.) Michx	Nepetin, jaceocidin and hispidulin aglycones, lippiflorin A and B glycosides, nodiflorin A and B,	Alkaloids, resin, sugars, stigmasterol, β -sitosterol	83, 38
<i>L. rehmanii</i> H.H.W. Pearson		Triterpenic compounds, icterogenin, rehmannic acid	41
<i>L. sidoides</i> Cham	6,7- dimethoxy-5,4 ^l -dihydroxyflavone	Naphthoquinoids, lapachenol, isocatalponol	58
<i>L. turbinata</i> Griseb		Leucoanthocyanidins, steroidic and triterpenic compounds, alkaloids and cardenolides (traces)	59

Oliviera and co-workers⁸³ described the preliminary stage for chemotyping of *Lippia* species to involve collection and drying of identified aerial parts of plant specimens. This was followed by extraction of essential oil from the leaves by hydrodistillation in a Clevenger-type apparatus for 4 hours with 1.5 L of water; with a good yield of about 1.0% v/w. The essential oil was dried with anhydrous sodium sulfate and stored at 4 °C. Analysis of extract was also carried out using the GC-MS technique⁶⁷.

Chemically, essential oil constituents belong to the following classification namely hydrocarbons, monoterpenes, oxygenated monoterpenes, sesquiterpenes, oxygenated sesquiterpenes, diterpenes, oxygenated diterpenes, triterpenes, oxygenated triterpene, aromatic compounds, alcohols, fatty acids, ketones and heterocyclic compounds^{85, 86, 87, 88, 89, 90}. Common chemotypes for *Lippia* essential oil are compiled in **Table 3**.

TABLE 3: MAIN ESSENTIAL OIL CHEMOTYPES OF LIPPIA SPECIES

Plants	Monoterpenes	Sesquiterpenes	References
<i>L. affinis aristata</i> Schau	Sabinene, limonene, p-cymene, α -pinene, γ -terpinene	β -caryophyllene, α -cadinene, γ -elemene	29 62
<i>L. adonensis</i> Hochst	α -terpineol, β -pinene, γ -terpinene, carvone, 1,8-cineole, p-cymene, limonene, linalool, thymol	δ -cadinene, β -caryophyllene, nerolidol, germacrene-D	62
<i>L. alba</i> (Mill.) N. E. Brown	Borneol, camphor, 1,8-cineole, geranial, myrcene, linalool, neral, sabinene	β -caryophyllene, β -elemene, γ -cadinene, α -muurolene	29 30 62
<i>L. citroidora</i> Kunth.	Citral- A, citral-B, geraniol, 1,8-cineole, linalool, limonene	Caryophyllene oxide	62 85
<i>L. dulcis</i> Trevir.	Camphor, camphene, limonene, terpinolene, α -pinene, lippiol	α -copaene, β -caryophyllene, δ -cadinene, (+)-hernandulcine	48 45,48 62 91
<i>L. gracilis</i> HBK	Thymol, cavacrol, p-cymene, 4-terpenil-acetate	α -copaene, β -cubebene	50
<i>L. graveolens</i> H.B.K	β -phellandrene, cavacrol, p-cymene, methylthymol, thymol	α -humulene, β -caryophyllene, β -bisabolene, aromadendrene	49

<i>L. javanica</i> (N.L Burm.) Spreng.	Myrcene, myrcenone, ocimene, (E)-tagetone, cis-tagetone	β -caryophyllene	62
<i>L. multiflora</i> Moldenke	1,8-cineole, linalool	Nerolidol	28
<i>L. nodiflora</i> (L.) Greene	2-phenethyl alcohol, 1-octen-3-ol, linalool, 2,6-dimethyloctane, methylsalicylate, p-cymen-8-ol	β -farnesene, β -caryophyllene, germacrene-D	62
<i>L. organoides</i> H.B.K	1,8-cineole, α -terpinene, γ -terpinene, p-cymene	Calamenene, β -caryophyllene, α -copaene, δ -cadinene, α -bergamotene, β -bisabolene, β -caryophyllene, umbellulone	62
<i>L. sidoides</i> Cham	p-cymene, cavacrol, α -terpinene, thymol	β -caryophyllene, umbellulone	50
<i>L. turbinata</i> Griseb	α -thujone, carvone, limonene, bornyl acetate, camphor	α -humulene	62
<i>L. ukambensis</i> Vatke	Terpineol, δ -3-carene, camphene, camphor, 1,8-cineole, p-cymene, trans-sabinene hydrate, terpinen-4-ol	β -caryophyllene oxide, β -cubebene, spanthulenol, β -caryophyllene, germacrene-D	62
		β -cubebene	51

The range of major volatile constituents reported in *Lippia* were hydrocarbons (pinene, limonene, isabolene), alcohols (linalol, santalol), acids (benzoic acid, geranic acid), aldehydes (citral), cyclic aldehydes (cuminal), ketones (camphor), lactones (bergaptene), phenols (eugenol), phenolic ethers (anethole), oxides (1,8 cineole) and esters (geranyl acetate)⁹². Most phytochemical studies of *Lippia* have concentrated on the chemistry of the volatile constituents, resulting in limited information being available on the non-volatile secondary metabolites⁹³.

The species of *Lippia* contain a varying number of chemotypes (depending on the geographical source), some of which contain more of particular chemotypes than the other. For example, *Lippia alba* has about 12 chemotypes, and GC analysis of essential oils from this specie reveals the predominance of monoterpene compounds such as citral, β -myrcene, limonene, and carvone. Three of the 12 chemotypes are iridoides; others include flavonoid glycosides and phenylethanoid glycosides⁹⁴.

Meanwhile, Monoterpenes such as limonene, carvone, citral, β -caryophyllene, tagetenone, myrcene, γ -terpinene, camphor, 1,8-cineole, and

estragole are frequently found in the essential oils of *L. alba*⁹⁵. Similarly, the essential oils of *Lippia multiflora* were characterized by richness in 1,8-cineole, sabinene, α -terpineol and α -pinene (out of at least 13 distinct chemotypes), most of which are distributed across Nigeria, Ghana and Togo⁶⁷. Kunle and Egharevba⁶⁶ gave a comprehensive review of the essential oil chemotypes found in *Lippia multiflora*. *L. organoides* was characterized by different chemical types: p-cymene, α - and β -phellandrene and limonene (chemotype A)⁹⁶, carvacrol (chemotype B)^{97, 87}, thymol chemotype C)^{98, 100}, 1,8-cineole (chemotype D)⁹⁹. Lately (*E*)-methyl cinnamate and (*E*)-nerolidol (chemotype E)¹⁰⁰ were identified by GC-MS analysis of *Lippia ukambensis* Vatke essential oil. Two chemotypes were identified by the camphor and 1,8-cineole in *Lippia ukambensis* Vatke on examination by GC/MS. On a separate note, the major compound in the oil of *L. somalensis* was 1, 8-cineole (31.9%)⁵¹. Structure of some compounds found in *Lippia* species is shown in **Fig. 3**.

It is noteworthy that some iridoid glycosides including theveridoside were isolated from *L. javanica* and were considered as chemotaxonomic markers for the genus *Lippia*. However, the reasons for chemotaxonomy included the following:

variable composition and structure of given determined chemical constituents; the percentage/ composition of any given compound in a plant would give the progression of a plant, species or

genus; variation in chemical constituents can be exactly described in terms of definite structural configuration, and provides a way to understand their biosynthesis¹⁰¹.

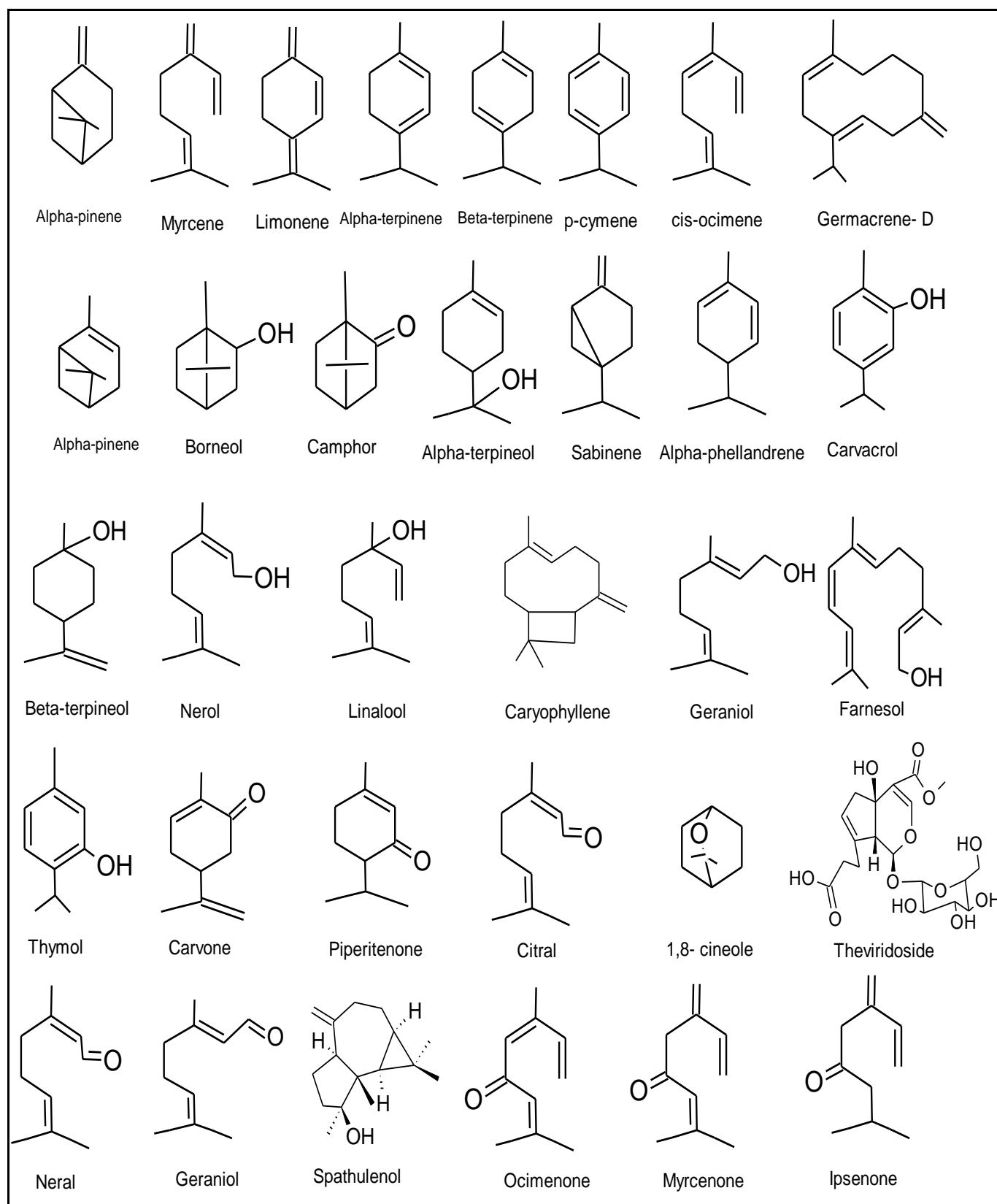


FIG. 3: STRUCTURE OF SOME COMPOUNDS FOUND IN *LIPPIA* SPECIES

CONCLUSION: The chemical compositions of *Lippia* species essential oils vary markedly giving rise to chemotypes. These depend on geographical factors, genetic factors, environmental conditions, nutritional status and the effects of mechanical damage or herbivory. By and large, limonene, p-cymene and β -caryophyllene cut across the essential oils of known species of *Lippia*, and could be considered chemotaxonomic markers. The chemical characterization of the oil is vital to determining the commercial value and potential application. Chemotypic variability is an essential factor in selecting essential oil-bearing medicinal plant for commercial development, especially in terms of chemical fingerprinting often required in quality control.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

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How to cite this article:

Okhale SE, Nwanosike EM, Fatokun OT and Kunle OF: Phytochemistry and Ethnopharmacology of *Lippia* Genus with a Statement on Chemotaxonomy and Essential Oil Chemotypes. Int J Pharmacognosy 2016; 3(5): 201-11. doi: 10.13040/IJPSR.0975-8232.3(5).201-11.

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