ORIGINAL ARTICLE
Discovery Phytomedicine 2020, Volume 7, Number 1: 19-26

Traditional uses, Physical properties, Phytochemistry and Bioactivity of *Lippia multiflora* Moldenke (Verbenaceae): A Mini-review

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ABSTRACT

In the Democratic Republic of the Congo (DRC), medicinal plants represent the main product for both urban and rural populations for their health care needs due to the high costs of conventional medicine. These plant species contain bioactive compounds also called phytochemicals that are capable of modulating metabolic processes and resulting in the promotion of better health. In the present paper, the aims were to give updated information on the physical properties, phytochemistry and pharmacological activities of *L. multiflora*, medicinal plant in Republic Democratic of the Congo (DR. Congo). A literature search of this specie was conducted to obtain information about the nutritional value, phytochemistry and biological activities from various electronic databases (PubMed, PubMed Central, Science Direct, Google scholar and Sci-hub). The chemical structures of *L. multiflora* naturally occurring compounds were drawn using ChemBioDraw Ultra 12.0 software package. In this study, the bibliographic references were using bibliographic software Mendeley. *L. multiflora* Moldenke is a tropical to subtropical herbaceous aromatic plant widely distributed in West and Central Tropical Africa. It has been traditionally used in ethnomedecine against various disorders. It has been reported that the essential oil composition of *L. multiflora* from some locations were characterized by high terpenoids content, in particular: 1,8-cineole, linalool, geranial and neral, ipsdienone and (Z)- and (E)-ocimenone, thymol and thymyl acetate, p-cymene, sabinene, α-terpineol, α-phellandrene, myrcene and epoxymyrcene, myrtenol, limonene, (E)- and (Z)-tagetone and ipsenone, nerolidol, geraniol, γ-terpinene, (E)-caryophyllene, and β-farnesene). Many study reported that the plant possess various biological properties like anti-hypotensive, anti-inflammatory, anti-analgesic, anti-pyretic, anti-malaria, anti-oxydant, anti-microbial activities. The present review can therefore help inform future scientific research towards the development of novel drugs of relevance from *L. multiflora* for the improvement of human health and wellbeing.

Keywords: *L. multiflora* Moldenke, medicinal plants, photochemistry and pharmacological activities.

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Cite This Article: Masunda, A.T., Inkoto, C.L., Masengo, C.A. Bongili, S.B., Basilua, J.K., Legbiye, E.M., Ngbolua, K., Mpiana, P.T. 2020. Traditional uses, Physical properties, Phytochemistry and Bioactivity of *Lippia multiflora* Moldenke (Verbenaceae): A Mini-review. *Discovery Phytomedicine* 7(1): 19-26. DOI:10.15562/phytomedicine.2019.114

INTRODUCTION

Background

Historically, plants have been used for the treatment and prevention of various illnesses. With the revolution of science, the popularity of herbal medicines has widened.[1,2] World Health Organization (WHO) reports that 80% of the world's population use herbal medicines for their primary healthcare.[3-7] In the Democratic Republic of the Congo (DRC), medicinal plants represent the main product for both urban and rural populations for their health care needs due to the high costs of conventional medicine.[4,6] These plant species contain bioactive compounds or phytochemicals that are capable of modulating metabolic processes and resulting in the promotion of better health. Some of these plants act therefore as functional foods and could serve as sources of nutraceuticals.[8] *Lippia multiflora* belonging to Verbenaceae family has diverse application, ranging from treatment of respiratory to gastrointestinal disorders. Indeed, *L. multiflora* has been traditionally used to treat disease conditions like bronchial inflammation, venereal disease, malaria, conjunctivitis, gastro-intestinal disturbance, enteritis, etc., because of the perceived antimicrobial properties.[9] It has been reported that the essential oil composition of *L. multiflora* from some locations were characterized by high terpenoids content, in particular: 1,8-cineole, linalool, geranial and neral, ipsdienone and (Z)- and (E)-ocimenone, thymol and thymyl acetate, p-cymene, sabinene, α-terpineol, α-phellandrene, myrcene and epoxymyrcene, myrtenol, limonene, (E)- and (Z)-tagetone and ipsenone, nerolidol, geraniol, γ-terpinene, (E)-caryophyllene, and β-farnesene.[10-15] Some other

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works[13,16-23] showed that this plant is used in Africa folk medicine for the treatment various disorders. Various study, confirmed the anti-hypotensive, anti-inflammatory, anti-analgesic, anti-pyretic, anti-malaria, anti-oxydant, anti-microbial activities and muscle relaxant, pedicucidal and scabicidal properties of the parts of this plant.

In the work reported in this paper, an attempt has been made to give updated information on the phytochemistry and pharmacognosy of this medicinal plant used in Republic Democratic of the Congo.

Botany and geographic distribution

L. multiflora Moldenke is a shrubby aromatic plant, growing up to 1.2 m with whitish flowers on cone-like heads in a terminal panicle, and nearly 12 mm long.[24] It is widely distributed in west and Central Tropical Africa.[25]

METHODOLOGY

In this study, a literature search was conducted to obtain all information about the traditional uses, physical properties, phytochemistry and bioactivity of *L. multiflora* Moldenke (Verbenaceae) from various electronic databases (PubMed, PubMed Central, Science Direct and Google scholar). The scientific name of this plant species was used as the keyword for the search. The chemical structures of the *L. multiflora* naturally occurring compounds were drawn using ChemBioDraw Ultra 12.0 software package but the bibliographic references were done using bibliographic software Mendeley.

RESULTS AND DISCUSSION

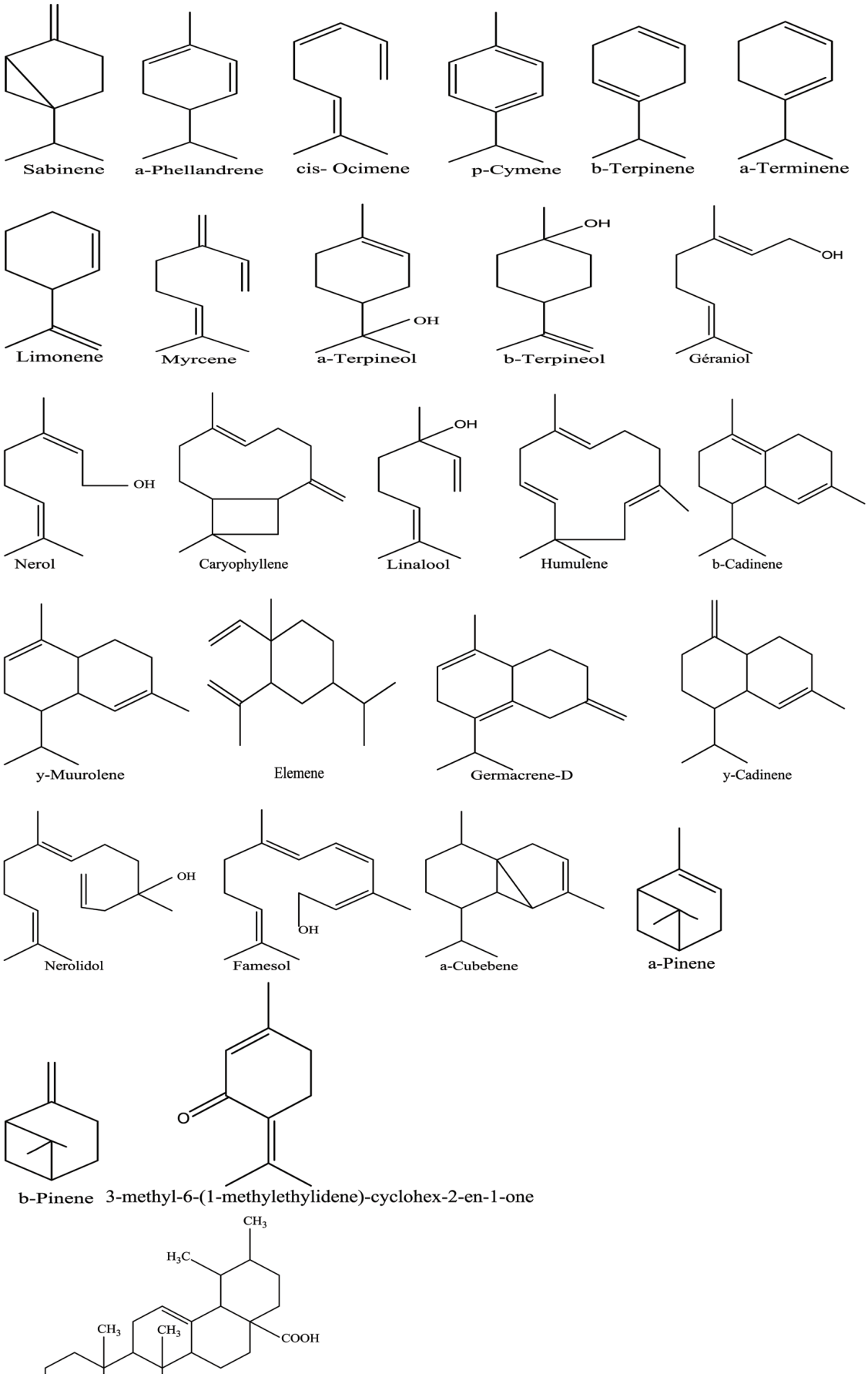
Ethno-medicinal uses

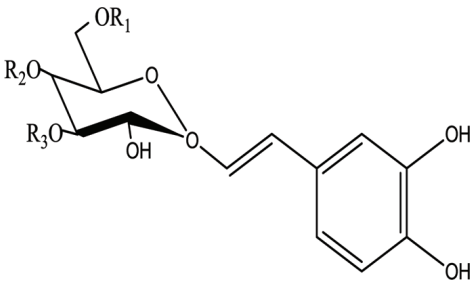
L. multiflora has a long history of traditional medicinal application some of which have scientific validation. This plant has a diverse application in ethnomedicine, ranging from treatment of respiratory and gastrointestinal disorders. *L. multiflora* has been traditionally used to treat disease conditions like bronchial inflammation, venereal disease, malaria, conjunctivitis, gastro-intestinal disturbance, enteritis, etc., because of the perceived antimicrobial properties.[9] Various study reported the plant exhibit anti-malarial, spasmolitic, sedative, hypotensive and anti-inflammatory activities.[26-29] Kanco et *al.*[30] and Pascual et *al.*[31] reported this plant has been used in many traditional and herbal medicines to treat bronchial inflammation, malaria fever, conjunctivitis, gastro-intestinal disturbance, enteritis, coughs and colds and possesses hypotensive, fatigue-relieving, and diuretic properties. The Tea-like infusions is given as a malaria fever while crushed leaves are used against stress, hypertension, conjunctivitis, venereal diseases and as a laxative.[32] The leaf infusion is also employed to treat a sudorific (diaphoretic) febrifuge. It forms part of various complex plant recipes for the treatments of sleeping sickness especially for severe jaundice.[33] In Nigeria, leaves are used for constipation and as a febrifuge (antipyretic). *L. multiflora* tea is commonly consumed in Northern Nigeria as remedy for malaria fever. In Ghana, the leaf infusion of sun-dried leaves is consumed as tea with sugar or honey for stomach ailments.[19,34] The study of Kunle et *al.*[33] reported that, In Gambia, local beehives are smoked with this fragrant plant to attract settling of bees. This plant was also used by children in the form of an ointment and also for treating fever and constipation.[34] Other traditional medicinal uses include its application as an antimalarial infusion and the treatment of respiratory disorders.[31]

Figure 1 Leaves and flowers of ***L. multiflora*** Moldenke (A); ***L. multiflora*** Moldenke conditioning before sale at the market (B)

Photochemistry

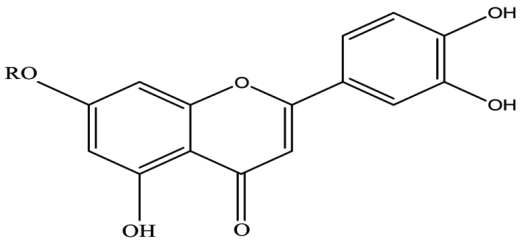
Some researchers have reported several known compounds and secondary metabolites. The phytochemical screening revealed the presence of almost the same phytochemical groups (cathetic and gallic tannins, flavonoids, anthocyanins, leucoanthocyanes, triterpenoids, mucilage, coumarins and the reducing compounds) in both leaves and flowers from all sites with variable abundances. Alkaloids were found only in leaves while steroids, quinone derivatives and combined anthracene C-heterosides were identified uniquely in flowers. Reports on the analysis of *L. multiflora* oil showed the presence of Carvacrol,[35] α-Thujene, α-Pinene, Sabinene, β-Pinene,1-Octene-3-ol, 6-Methylhept-5-en-2-one, Myrcene, 3-Octanol, α-Phellandrene, α-Terpinene, p-Cymene, β-Phellandrene, 1,8-Cineole, (Z)-β-Ocimene, γ-Terpinene, cis-Sabinene hydrate, Terpinolene, Linalool, Menth-2-en-1-ol,Citronnellal, δ-Terpineol, Terpinene-4-ol, α-Terpineol, Nerol, Neral, Geraniol, Geranial, Thymol, Carvacrol, α-Cubebene, Thymyl acetate, Eugenol, Neryl acetate, Carvacryl acetate,


Sabinene
a-Phellandrene
cis- Ocimene
p-Cymene
b-Terpinene
a-Terminene
Limonene
Myrcene
OH
a-Terpineol
OH
b-Terpineol
OH
Géraniol
OH
Nerol
Caryophyllene
OH
Linalool
Humulene
b-Cadinene
y-Muurolene
Elemene
Germacrene-D
y-Cadinene
OH
Nerolidol
OH
Famesol
a-Cubebene
a-Pinene
b-Pinene
O
3-methyl-6-(1-methylethylidene)-cyclohex-2-en-1-one
CH3
H3C
CH3
CH3
COOH



Verbascoside (acteoside): R1 = H, R2 = (E)-caffeoyl, R3 = á-L-rhamnoside
Isoverbascoside (isoacteoside): R1 = (E)-caffeoyl, R2 = H, R3 = á-L-rhamnoside
Nuomioside A (calceolarioside E, cusianoside A): R1 = H, R2 = (E)-caffeoyl, R3 = â-D-apioside
Isonuomioside A: R1 = (E)-caffeoyl, R2 = H, R3 = â-D-apioside

CH_3-$(CH_2)_{31}$-CH_3
n-tritriacontane



Luteolin: R = H
Luteolin-7-O-glucuronide: R = â-D-glucuronide

Figure 2 Selected compounds isolated from the essential oils of ***L. multiflora***

Table 1 Volatile components of *L. multiflora* Moldenke essential oil[22]

Rr (min)	Identification	Percentage of total oil
09.8	Sabinene I	0.3
10.3	Myrcene	0.2
10.7	α-Phellandrene	1.8
11.3	Para-Cymene	0.2
11.5	1,8-Cineole	3.1
11.5	Limonene	0.2
13.6	Linalool	20.2
16.4	α-Terpineol	0.3
17.3	Nerol	0.4
22.2	α-copaene	0.3
22.4	β-Bourbonene	0.3
23.5	β-Carophyllene	3.8
24.2	(Z)b-Farnesene	10.5
24.4	α-Humulene	0.4

α-Copaene, β-Bourbonene, Geranyl acetate, β-Cubebene, β-Caryophyllene, α-Humulene, (E)-β-Farnesene, Alloaromandendrene, Germacrene D, α-Muurolene, β-Bisabolene, Cubebol, δ-Cadinene, Nerolidol, Caryophyllene oxide, Guaiol, Humulene II oxide, Aromandendrene oxide, epi-α-Cadinol, Germacra-4(15), 5,10(14)-Trien-1-ol.[18,36] Alexis et *al.*[22] reported that essential oil of *L. multiflora* was characterized by a high content in linear terpenes: nerolidol (45.2%), linalool (20.2%) and β-farnesene (10.5%); germacrene D, β-caryophyllene and 1-8-cineol were important minor components. Table 1 give volatile components of *L. multiflora* essential oil and figure 2 gives structures of selected compounds.

Physico-Chemical Properties Of Essential Oil

Kunle et *al.*[9] reported in literature, the reports on the physical properties of the oil are limited and vary widely. The variability is thought to be as a result of variation in chemical component due to

Table 2 **Extract, model system used, pharmacological properties and plant part of biologically active compounds of *L. multiflora* Moldenke**

Part of plant	Extract uses	Molecules	Biological properties	Biological model	References
Leaves	Aqueous Extract methanolic extract	acetic acid	Analgesic effect	Male wistar rats and Swiss mice	[35]
		-	Antipyretic	Male wistar rats and Swiss mice	[35]
		-	Anti-inflammatory	Male wistar rats and Swiss mice	[35]
		Isonuomioside A, isoverbascoside, verbascoside, nuomioside A, caffeic acid, rosmarinic acid	Antioxidant activity	-	[20]
		-	Muscle relaxant properties	Mice and rats.	[21]
		essential oil	Antimalarial activity	*P. falciparum, A. gambiae, A. aegypti*	[13,22]
			Hypotensitive effects	-	[37]
	essential oil extract	terpineol and α- and β-pinene.	Pediculocidal and Scabicidal properties	-	[18]
		Carvacrol, thymol, elemol, 1,8-cineole, camphor, *para*-cymene	Antimicrobial properties	*S. aureus, E. hirae, C. albicans, S. cerevisiae, rats*	[16,17,19,23,38]
leaves and flowers		Cathetic and gallic tannins, flavonoids, anthocyanins, leucoanthocyanes, triterpenoids, mucilage, coumarins, alkaloids, steroids, quinone, anthracene.	Toxicity degree	Rats	[39]

geographical cultivation and other environmental and genetic factors.[24] Oladimeji et *al.*[19] and Juliani et *al.*[14] reported a widely varied yield for the oil. In a study of the seasonal variability of the oil yield from the plant in the authors' laboratory, it was revealed that the plant exhibits seasonal variability in its oil content between January and June with the highest yield of 1.57% in June.[33]

Biological Activities

Biological activities of extracts and molecules of L. multiflora are summarized in table 2.

Antimalarial activity

Alexis et *al.*[22] reported that the oil of *L. multiflora* was tested for antimalarial activity on *in vitro* cultures of *Plasmodium falciparum* (FcB1-Columbia chloroquine-resistant strain and F32-Tanzania chloroquine-sensitive strain). The dilutions inhibiting the *in vitro* growth of the parasite by 50% 24 and 72 hr after administration of the essential oil to the parasite culture were 1/12000 and 1/21000, respectively. When tested on a highly synchronized culture, the essential oil inhibited growth mostly at the trophozoite-schizont step, indicating a potential effect on the first nuclear division of the parasite.

Muscle relaxant properties

Noamesit et *al.*[21] reported, aqueous leaf extracts of this specie administered intraperitoneally produced a profound calming effect, muscle relaxing action, and significant reduction in the spontaneous locomotor activity of mice measured in the Ugo Basile activity cage. The extract (0.25-1.0 g Kg^{-1} reduced amphetamine induced locomotor activity in mice. The extract (0.5-1.0 mg ML^{-1}) inhibited contractions of the isolated rat diaphragm in response to the phrenic nerve stimulation. The muscles relaxant effect was considered to be primarily responsible for the calming effect, bordering on tranquilizing activity observed in mice and rats. In another work, a lyophilisated powder obtained from an infusion of dried leaves of *L. multiflora* Moldenke caused a muscle relaxant effect (in the traction test).[28]

Analgesic and antipyretic properties

Abena et *al.*[35] reported that at the doses used (2, 4 and 8 mL/kg o.s.) the essential oil of *L. multiflora* showed significant and dose-dependent analgesic effect on acetic acid-induced writhing in mice. Only the dose of 8 mL/kg of essential oil, antagonized hyperexia induced by brewer's yeast. No effect on granuloma formation was observed. In another work, Abena et *al.*[40] demonstrated that the

essential oil exhibited more analgesic activity than the crude extract while the crude extract was more effective as a muscle relaxant.[40] An analgesic activity (by using acetic acid and hot plate methods), but did not cause modification of rectal temperature.[28]

Antimicrobial properties

The essential oils were also tested against 09 strains using a broth micro-dilution method. The Gram negative bacteria were the most sensitive. The essential oil of this plant was the most active.[38] The antimicrobial activity of carvacrol and thymol, which were the major components of the oil has also been reported.[23,17] Mevy et *al.*[16] reported the oil exhibited strong inhibitory effect on the growth of *Staphylococcus aureus* and *Enterococcus hirae*, and a moderate effect was observed for *Candida albicans* and *Saccharomyces cerevisiae*.

Hypotensive effects

In a previous study, the hypotensive effects of *L. multiflora* were confirmed, its methanolic extract was found to be more active than its aqueous extract in normotensive rats.[27] In the Ivory Coast, *L. multiflora* is used as an infusion for the treatment of hypertension.[41]

Sedative effect

Additionally, the essential oil of *L. sidoides* Cham., the infusion of *L. multiflora* Moldenke and different *L. alba* (Mill.) N.E. Brown extracts, shows a sedative effect.[28,42,43]

Antioxydant activity

Hanson et *al.*[20] reported the on-line DPPH (2, 20-diphenyl-1-picrylhydrazyl radical) scavenging assay (reaction time = 0.45 s) applied to the infusion in "quantitative" mode, showed the relative order of activity: isonuomioside A > isoverbascoside > verbascoside > nuomioside A. In the microplate assay (reaction time = 2 h), isover- bascoside and verbascoside had similar activity. Both compounds were less active in the latter assay than the well-known flavan-3-ol antioxidant, (-)-epigallocatechin gallate, but more active than caffeic acid and an ester, rosmarinic acid. Steam pasteurisation of *L. multiflora* leaves at maximum exposure (150 s at ca 99°C) for improved microbial quality did not decrease the soluble solids content, phenolic content and antioxidant activities of the infusion compared to the untreated control ($p < 0.05$).

Anti-inflammatory activity

Various study demonstrated two monoterpenes (thymol and citral) have anti-inflammatory properties both *in vitro* and *in vivo*. This pharmacological activity is based on : inhibition of NF-kappa-B pathway activation, decreased expression of iNOS (inducible nitric oxide synthase), decreased NO (nitric oxide) production and NO scavenging.[44-46] Therefore the anti-inflammatory effects of two essential oils with different chemotypes derived from *L. multiflora* Mold harvested during March 2012 were examined, upon activated macrophages using nitric oxide (NO) as a biological marker

Scabicidal activity

In Nigeria, scabicidal activities of two topical emulsion formulations (Lippia oil emulsions A and B), each containing 20% w/w essential oil of *L. multiflora* , were compared with that of benzyl benzoate emulsion BP using randomized, double blind and group parallel studies. The percentage cure obtained for Lippia oil emulsion A were 50%, 80% and 80% on application for 3, 5 and 7 days, respectively, compared with 30%, 60% and 70% obtained for benzyl benzoate emulsion BP for the same treatment periods. There was no significant difference between the percentages of scabietic subjects cured with the two formulations (A and B) of Lippia oil ($P > 0.05$). Six adverse effects were reported for the Lippia oil emulsions, while 10 adverse effects were reported for benzyl benzoate emulsion BP. Since the Lippia oil emulsions were more effective and better tolerated than the benzyl benzoate emulsion, they were considered as additional formulations for the treatment of scabies.[19] The lethal effect of the lippia oil on headlice was increased when applied in an enclosed system that prevented volatilization of the oil while allowing maximum contact of the vapour with the headlice. A 20% v:v preparation of lippia oil applied to scabietic subjects for 5 consecutive days gave 100% cure compared with 87.5% cure obtained for benzyl benzoate preparation of the same concentration. The GC-MS analysis of oil revealed, among others, the presence of terpineol, a- and b-pinene which are known to be lethal to body and headlice.[18]

Toxicity degree of lippia multiflora

Djengue et *al.*[39] reported the extracts from both leaves and flowers showed positive action on shrimp larvae but with CL50 of (13.28±1.52 mg/mL for leaves; 0.46±0.05 mg/mL for flowers) superior to 0.1mg/mL, hence indicating the non-toxicity of *L. multiflora*.

CONCLUSION

The plant species contain bioactive compounds that are capable of modulating metabolic processes and resulting in the promotion of better health. In the present mini-review, the aim was to give updated information on the traditional uses,

physical properties, phytochemistry and pharmacological activities of *L. multiflora*, medicinal plant in Republic Democratic of the Congo (DR. Congo). The literature survey revealed that *L. multiflora* is a pharmacologically and chemically much studied plant species, although the diversity of secondary metabolites present in this plant species is enormously various.

ACKNOWLEDGEMENT

The authors gratefully acknowledge and thank the TWAS and the Swedish International Development Agency (SIDA) for the grant

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