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Chemical composition and antiproliferative activity on prostate and cervical cancer cell lines of *Lantana camara* Linn. essential oil

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ABSTRACT

Lantana camara (LC) is an aromatic plant used in traditional medicine in Burkina Faso in association with other plants for the management of many microbial and inflammatory pathologies. The objective of this study was to determine the chemical composition, the antioxidant and antitumor activities on prostate and cervical cancer cells in culture of the essential oil (EO) of this plant. The chemical composition of *Lantana camara* EO was determined by Gas Chromatography with Flame-Ionization Detection (GC-FID) and Gas Chromatography–Mass spectrometry (GC-MS) analysis and the antiproliferative activity was evaluated through the 3[4.5-dimethylthiazol-2-yl]-diphenyltetrazolium bromide (MTT) test assay. A total of 48 compounds have been identified in the essential oil of *Lantana camara* of which cabinene, beta-caryophyllene, eucalyptol and alpha-humulene are found to be the majority. However, 4 compounds, unknown in the literature, present in this essential oil have not been identified. *Lantana camara* essential oil inhibits both the proliferation of HeLa cells from cervical cancer and LNCaP (Lymph Node Carcinoma of the Prostate) cells from prostate cancer. Beyond constituting the scientific basis for the use of *Lantana camara* in traditional medicine through its antiproliferative effect. These results require further study by determining the nature of its unidentified compounds and its mechanism of molecular action on these two cancer cell lines *in vitro*.

Keywords: *Lantana camara*, Essential oil, Chemical composition, Cancer.

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INTRODUCTION

Cancer is a major public health problem and the second leading cause of death worldwide (Puyol et al., 2021). The burden of cancer continues to grow and is expected to double unfortunately by 2040 (Puyol et al., 2021). Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer death in women (Bray et al., 2018). Worldwide, prostate cancer is the second most common solid tumor in men (Gandaglia et al., 2021). The treatment of these pathologies remains expensive and inaccessible, especially for populations in developing countries. Therefore, it is mandatory to screen all the possible cost-effective options for better care of people suffering from cancer in general and from prostate and cervical cancer, in particular. One of the appropriate options may be natural molecules and extracts from plants, which have been shown in several studies to have anti-cancer activity (Samarakoon et al., 2014; Sriwiriyajan et al., 2014; Nasr et al., 2018; Omara et al., 2020; Buranrat et al., 2020; Bayala et al., 2020; Díaz et al., 2022). Otherwise, several studies have already shown the various anticancer properties of essential oils, volatile substances extracted from aromatic plants (Niksic et al., 2021; Ruttanapattanakul et al., 2021; Yeh and Lin, 2021; Khalil et al., 2021). *Lantana camara* is an aromatic plant used in traditional medicine in Burkina Faso and whose essential oil has antimicrobial, antioxidant (Udappusamy et al., 2022) and cytotoxic (Barros et al., 2016) properties.

Lantana camara Linn. is traditionally used for its many medicinal properties including antibacterial (Kirimuhuzya et al., 2009; Dehou et al., 2021), antimalarial, anticancer and anti-inflammatory (Dougnon and Ito, 2020).

The aim of this study was therefore to determine the chemical composition and the anti-proliferative activity of the essential oil of *Lantana camara*, a medicinal plant used in Burkina Faso in the treatment of bacterial and inflammatory diseases.

MATERIALS AND METHODS

Plant material and extraction of essential oil

Lantana camara leaves (Figure 1) were collected in Ouagadougou, Burkina Faso; GPS location: 12°25’29.5’’N and 1°29’14.3’’W. Fresh leaves (1 kg) were subjected to hydro distillation using a still/Clevenger type apparatus for 3 hours (Bayala et al., 2018). The extracted EOs were then stored in airtight containers in the refrigerator at 4°C until the GC-FID and GC/MS analysis and the biological tests. EOs were diluted in hexane (1/30. v/v) for GC/FID and GC/MS analysis.

Chemical composition

Flame Ionization Detector Gas Chromatography (GC/FID) analysis

The composition of EOs was carried out as mentioned previously (Bayala et al., 2014b). Briefly. the gas phase chromatography of EO diluted in hexane was carried out on an Agilent model 6890 gas phase chromatograph (Agilent, Palo Alto, California), equipped with a 30 m x 0.25 mm column, with a film thickness of 0.25 µm under hydrogen flow, from 50°C (5 min) to 300°C with an increasing temperature of 5°C/min. The sample was injected in split mode, with injector and detector temperatures 280 and 300°C, respectively (Bayala et al., 2018).

Gas Chromatography coupled with mass spectrometry (GC/MS) analysis

Mass spectrometry analyzes were also carried out as described above (Bayala et al., 2014b). Briefly, an Agilent Model 7890 Gas Chromatograph coupled to an Agilent MS Model 5975 was used. Helium was used with an average flow rate of 1.0 mL/min. The oven temperature program ran from 50°C (3.2 min) to 300°C at 8°C/min, 5 min after running at 300°C. The sample was injected in split mode, with the temperature of the injector and the

detector being 250°C and 280°C respectively (Bayala et al., 2018). The MS operating in electron impact mode at 70eV; electron multiplier, 1500V; ion source temperature, 230°C; mass spectra data were acquired in sweep mode in the range m/z 33-450 (Bayala et al., 2018).

Identification of compounds

The compounds present in the essential oil of *Lantana camara* were identified as described previously (Bayala et al., 2014b). Using standard compounds to identify essential oil components would have been the state-of-the-art methodology. However, due to technical and resource constraints, we performed retention indices and comparisons with the NIST library. (Stein et al., 2002) or literature (Adams, 2007). Relative percentages of compounds were calculated based on GC peak areas without using correction factors (Bayala et al., 2018).

Culture of cells

One human prostate cancer cell line and one cervical cancer cell line were used.

LNCaP cell line is an androgen-responsive prostate cancer cell line with low metastatic potential derived from lymph node metastasis (Horoszewicz et al., 1983).

The HeLa cervical cancer cell line come from a sample of metastases from an African-American patient named Henrietta Lacks with cervical cancer who died in 1951 (Culliton, 1974). These cells are available at LABIOGENE (Laboratoire de Biologie Moléculaire et de Génétique) by Genetics. Reproduction and Development (GReD) Laboratory of Clermont-Auvergne University, France. They were cultured and maintained at 37°C in a chamber humidified with 5% CO_2 in 75 cm^2 tissue culture flasks, in medium supplemented with 10% fetal calf serum (FCS, Biowest Nuaillé, France), 1% penicillin and 1% streptomycin (Invitrogen, Oslo, Norway). The LNCaP cells were maintained in RPMI-1640 medium (Invitrogen) and HeLa cells in DMEM (Dulbecco's Modified Eagle Medium) (Invitrogen).

Antiproliferative activity

The 3[4.5-dimethylthiazol-2-yl]-diphenyltetrazolium bromide assay (Sigma-Aldrich) (MTT) was used to measure cell viability. Briefly, 50.000 cells / mL were seeded for 24 h in 96-well plates. After 24 hours, *Lantana camara* essential oil was added. And after 72 h of incubation, the number of live cells was determined (Bayala et al., 2014b, 2018) using a Bio-Rad 11885 type microplate reader at 490 nm. The experiments were carried out in sextuplets three times in a row on each cell line.

Statistical analyses

In vitro experiments were performed in sextuplets, with each data point representing the mean of at least three independent experiments. All data are presented as mean ± standard deviation. Data were analyzed by analysis of variance followed by Tukey multiple comparison test. Analyzes were performed using XLSTAT 7.1 software. $P < 0.05$ was used as the criterion for statistical significance.

Figure 1: Photo of *Lantana camara*.
This photograph of *Lantana camara* was taken by Dr Bagora BAYALA in Ouagadougou, Burkina Faso. GPS location: 12°25'29.5''N and 1°29'14.3''W.

RESULTS

Chemical composition:

Analysis of the essential oil from the leaves of *Lantana camara* (Figure 1) showed that this plant contained a diversity of chemical compounds (Figure 2). Indeed, forty-eight (48) compounds were been identified in the essential oil of *Lantana camara* at a total rate of 96.57% (Table 1) including four (4) compounds not known in the literature. These secluded compounds Unknown MW 220; 32.05 (0.98%), Unknown MW 220; 32.61 (2.58%), Unknown MW 220; 33.07 (0.93%) and Unknown MW 226; 33.49 (0.73%). The major compounds of *Lantana camara* essential oil were: Sabinene (20.38%), β-Caryophyllene (17.88%), Eucalyptol (10.56%), α-Humulene (6. 68%), Bicyclogermacrene (4.46%) and α-piene (3.36%) as presented in Table 1.

Anti-Proliferative Activity

The results of the effect of *Lantana camara* essential oil on human prostate cancer LNCaP cell lines and cervical cancer HeLa cell lines are shown in Table 2. Lantana camara exhibited an inhibitory concentration 50 (IC50) of 130.72 ± 8.31 µg / mL on Prostate cancer LNCaP cells and 229.27 ± 11.25 µg / mL on cervical cancer HeLa cells after 72 hours of induction. Figure 3 shows the variation in the antiproliferative activity of the essential oil of *Lantana camara* as a function of the concentration used.

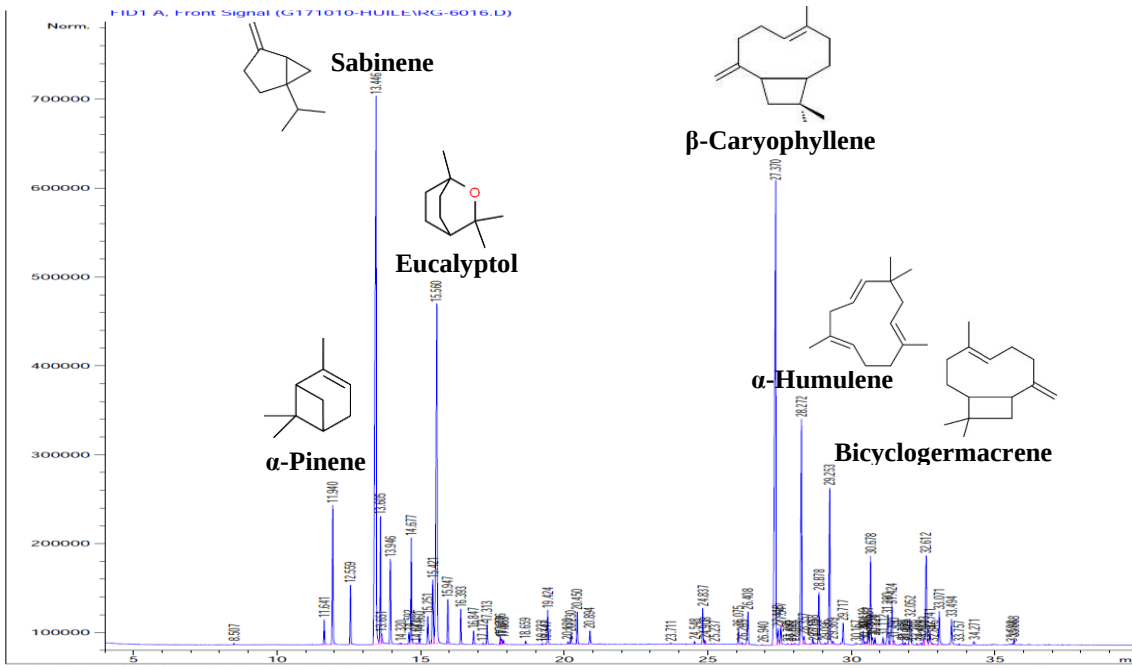

Figure 2: Chromatogram of chemical analysis of *Lantana camara* essential oil.
The names and molecules of the major compounds have been shown on the chromatogram.

Table 1: Chemical composition of *Lantana camara* essential oil.

Compound	Retention time (min)	Percentage (%)
α-Thujne	11.64	0.57
α-Pinene	11.94	3.36
Camphene	12.56	1.40
Sabinene	13.45	20.38
β-Pinene	13.60	2.78
1-Octene-3-ol	13.65	0.24
Myrcene	13.95	1.92
α-Phellandrene	14.59	0.29
Delta-3-Carene	14.68	2.48
α-Terpinene	14.96	0.22
Para-Cymene	15.25	0.75
Limonene	15.42	2.14
Eucalyptol	15.56	10.56
(E)-β-Ocimene	15.95	0.99
γ-Terpinene	16.39	0.79
Cis-Linalool Oxide	16.85	0.32
Terpinolene	17.31	0.46

Linalol	17.78	0.18
Pentyl 3-Methyl-Butanoate	17.82	0.12
Allo-Ocimene	18.66	0.09
Hexyl Iso-Butanoate	19.23	0.03
Camphre	19.42	0.83
Delta-Terpineol	20.13	0.06
Borneol	20.23	0.25
Terpinene-4-ol	20.45	0.76
α-Terpineol	20.89	0.32
Delta-Elemene*	24.84	0.85
Delta-Elemene *	24.91	0.10
α-Copaene	26.08	0.38
7-Epi-Sesquithujene	26.20	0.05
Delta-Elemene	26.41	1.02
β-Caryophyllene	27.37	17.88
γ-Elemene	27.45	0.47
β-Copaene	27.55	0.47
(Z)-Béta-Farnesene	27.92	0.03
α-Humulene	28.27	6.68
Gamma-Muurolene	28.66	0.17
Germacrene-D	28.88	1.30
Bicyclogermacrene	29.25	4.46
Delta-Cadinene	29.72	0.61
(E)-Nerolidol	30.68	2.21
Germacrene-D*	30.83	0.19
Spathulenol	31.28	0.91
Caryophyllene Oxide	31.42	1.28
Inconnu MW 220	32.05	0.98
Inconnu MW 220	32.61	2.58
Inconnu MW 220	33.07	0.93
Inconnu MW 226	33.49	0.73
Total		**96.57**

Hydrocarbon monoterpenes	38.63
Hydrocarbon sesquiterpenes	34.66
Oxygenated monoterpenes	12.13
Not determined (unknown)	5.23
Others	5.94

*, Isomer not identified; MW, Molecular Weight.

Table 2: IC50 (µg/mL) of *Lantana camara* EO on LNCaP prostate cancer and HeLa cervical cancer cell lines.

	EO of *Lantanna camara*	
	LNCaP cells	HeLa cells
IC50 (µg/mL)	130.72 ± 8.31**	229.27 ± 11.25

Values are expressed as mean values ± standard deviation; n = 3 independent experiments in sextuplets; **, $p < 0.05$; significantly different values compared. EO, essential oil.

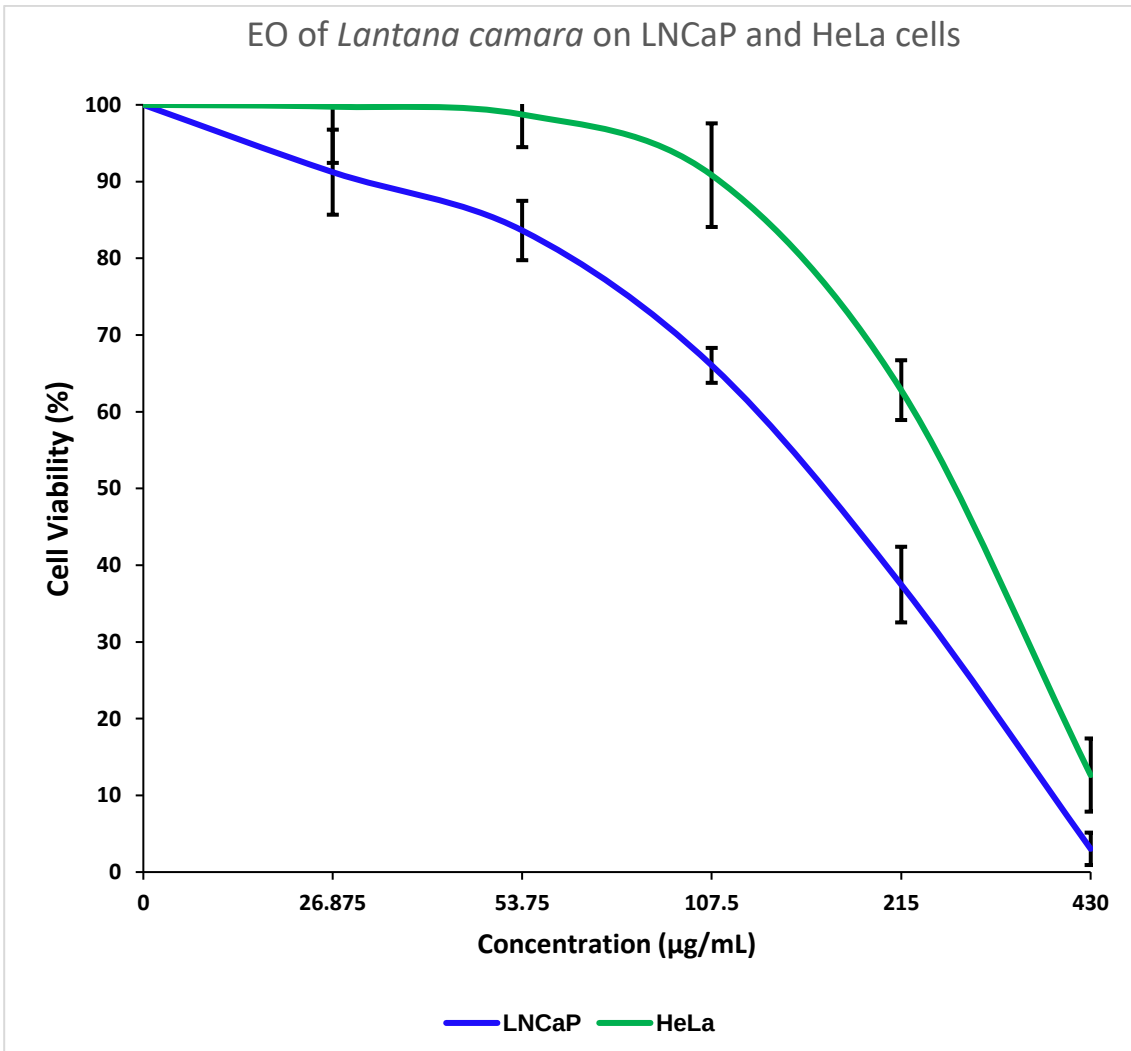

Figure 3: Dose-dependent antiproliferative activity of *Lantana camara* essential oil on LNCaP prostate cancer and HeLa cervical cancer cell lines.

The experiments were carried out three times in a row in sextuplets. The cells were treated 24 hours after seeding and revealed 72 hours after treatment.

DISCUSSION

A mixture of complex molecules (Bayala et al., 2014a), essential oils are complex, volatile and fragrant natural molecules synthesized by the secretory cells of aromatic plants (Duquénois and Anton, 1968). Chemical analysis of essential oil from *Lantana camara* leaves extracted by hydrodistillation showed that this plant contains a diversity of chemical compounds and groups of chemical compounds. Among the forty-eight compounds identified in the essential oil of *Lantana camara*, four were not yet known in the literature and the NIST library database used. These compounds would undoubtedly be new chemical compounds not yet identified and inventoried. With regard to the main compounds identified in the essential oil of *Lantana camara* leaves from Burkina Faso, there is a quantitative and qualitative difference compared to the one from Brazil. The main compounds of which were (E)-caryophyllene (23.75%), bicyclogermacrene (15.80%), germacrene D (11.73%), terpinolene (6.1%) and sabinene (5.92%) (Barros et al., 2016). This quantitative and qualitative difference between the essential oil of the leaves of *Lantana camara* from Burkina Faso and from Brazil could be explained by the geographical variation and the climate which can have an effect on the chemical composition. It could also be explained by several factors, including genetics, age, harvest season and/or plant environment (Letort et al., 2008; Gratani, 2014). The various chemical compounds identified showed that the essential oil of this medicinal plant from Burkina Faso was essentially composed of Monoterpene hydrocarbons (38.63%), Sesquiterpene hydrocarbons (34.66%) and Monoterpene alcohols (12.13%). However, a study carried out in Benin indicated the predominance of monoterpene hydrocarbons (60.58%) and oxygenated monoterpenes (33.39%) among which sabinene (38.81%) and 1.8- cineole (28.90%) (Dougnon and Ito, 2020).

Cancer research is an important step in cancer prevention and treatment strategies (Puyol et al., 2021). The essential oil of *Lantana camara* is antiproliferative. Indeed, its inhibitory concentrations 50 (IC50) on human prostate cancer cell lines LNCaP and HeLa for cervical cancer were respectively 130.72 ± 8.31 µg / mL and 229. 27 ± 11.25 µg / mL after 72 hours of induction. Prostate cancer LNCaP cells were more sensitive to *Lantana camara* essential oil than cervical cancer HeLa cells. In addition, the antiproliferative activity of the essential oil of *Lantana camara* according to the concentration was dose-dependent both on the LNCaP lines of prostate cancer and on the HeLa lines of cervical cancer. Other studies have demonstrated the anti-cancer effect of *Lantana camara* extracts. *Lantana camara* extract induced cell death of MCF-7 breast cancer cell lines (Han et al., 2015). It was also found through other scientific work that apoptosis induced by treatment with *Lantana camara* extract was regulated by the Bcl-2 family (Han et al., 2015). Bid and Bax were increased and Bcl-2 was decreased by *Lantana camara* extract. This extract also modulated the cleavage of caspase-8 and caspase-9. as well as poly (ADP-ribose) polymerase, PARP (Han et al., 2015). Furthermore, pentacyclic triterpenoids separated from *Lantana camara* leaves induced cycle arrest in breast cancer cell line MCF-7 *in vitro* (Shamsee et al., 2019). *Lantana camara* leaf lectin also showed a dose- and time-dependent inhibitory effect on colon cancer HT-29 cells with an IC50 of 3.75 µg / mL at 48 hours (Hiremath et al., 2020).

Conclusion

Lantana camara is commonly used in traditional medicine alone or in combination with other medicinal plants for the management of various diseases, mainly bacterial and inflammatory diseases in Burkina Faso. This study was aimed at determining the chemical composition of its essential oil extracted by hydrodistillation and to screen its anti-proliferative activity on LNCaP prostate cancer and HeLa cervical cancer cell lines. These preliminary results, obtained in this study, pave the way for a more in-depth investigation of *Lantana camara* essential oil. This investigation may be orientated, especially toward the determination of the nature of its unidentified compounds and its

mechanism of molecular action on the LNCaP cells of prostate cancer where it has a better activity.

COMPETING INTERESTS

The authors declare that there is no competing interests.

AUTHORS' CONTRIBUTIONS

BB, LLC, JS and JML designed the research; BB, LLC and GF performed the experiments. BB. LLC and LZ analyzed the data. BB, LLC, LZ, PFIZ, EO, FWD, AY, SB, JML and JS wrote the manuscript. All authors read and approved the final manuscript.

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