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BIOLOGICAL SCIENCES

Chemical composition and biological activities of the essential oils from *Vitex-agnus castus*, *Ocimum campechianum* and *Ocimum carnosum*

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Abstract: The essential oils obtained by hydrodistillation from fresh leaves of *Vitex agnus-castus* and *Ocimum campechianum*, and from fresh inflorescences of *Ocimum carnosum* were analysed by GC-FID and GC-MS. The major components of *V. agnus-castus* essential oil were identified as 1,8-cineole (47.9%), terpinyl α-acetate (11.6%), sabinene (11.2%) and caryophyllene oxide (9.7%), while in the *O. campechianum* essential oil were eugenol (72.1%), β-elemene (6.8%), (*E*)-caryophyllene (6.4%) and bicyclogermacrene (5.2%). Linalool (79.0%), α-*epi*-cadinol (5.4%), terpinen-4-ol (3.2%) and 1,8-cineole (2.8%) were the major constituents in the *O. carnosum* essential oil. The essential oils were subsequently evaluated for their larvicidal and cytotoxic activities. Larval bioassay against *Aedes aegypti* of *V. agnus-castus*, *O. campechianum* and *O. carnosum* essential oils showed LC_{50} values of 97.55 ± 0.35, 81.45 ± 0.35 and 109.49 ± 0.35 µg/mL, respectively. The in vitro cytotoxic activities of the essential oils has been evaluated on breast adenocarcinoma (MCF-7), lung carcinoma (NCI-H292), pro-myelocytic leukemia (HL-60), and cervical adenocarcinoma (HEP-2) human cell lines, and pro-myelocytic leukemia cells lines (HL-60) were found to be the most sensitive to all the essential oils tested than the others. This is the first report on larvicidal and cytotoxic activities of these essential oils.

Key words: *Aedes aegypti*, Cytotoxic activity, Lamiaceae, Larvicidal activity.

INTRODUCTION

Aedes aegypti Linnaeus (Diptera: Culicidae) is the main vector of dengue, chikungunya, and Zika virus. This species is widely distributed in the tropical and subtropical countries, where environmental and climatic conditions of temperature and humidity allow its proliferation (Jansen & Beebe 2010, Fujiwara et al. 2017). In addition, the geographical range of *Ae. aegypti* is increasing due to rapid urbanization and increased global movement of people and cargo (AlShebly et al. 2017). There are no specific drugs for the treatment of these diseases; therefore, the best strategy available to reduce the incidence of these viral diseases is the control of the insect vector (Moreira et al. 2016). Synthetic insecticides and insect growth regulators are widely used to reduce larval instars of mosquitoes. However, the frequent use of these insecticides can result in insecticide resistance, environmental pollution, and risks to human and other organisms (AlShebly et al. 2017).

Cancer is a disease that contributes to the uncontrolled growth and invasion of the abnormal cells leading to the formation of tumor, and is one the major causes of death worldwide. Chemotherapy is an important cancer treatment. However, the high cost, increasing multidrug resistance, and side effects direct the search for alternative chemotherapeutic agents (Gautam et al. 2014, Campos-Xolalpa et al. 2017).

Plants essential oils can be used as alternative sources of *Ae. aegypti* larval control agents (Aguiar et al. 2010, Gois et al. 2011, Dias & Moraes 2014, Pavela 2015, Carvalho et al. 2016, De Sousa et al. 2016, Mendes et al. 2017, Nascimento et al. 2017, Mar et al. 2018), and have been reported to show cytotoxic activity when tested on human cancer cell lines (Gautam et al. 2014, Lesgards et al. 2014, De Sousa et al. 2016, Kumar et al. 2016, Saleh et al. 2017, Tavakoli et al. 2017, Vasilijevic et al. 2018).

In this context, this study reports the larvicidal and cytotoxic activities of the essential oils from leaves of *Vitex agnus-castus* L. (Lamiaceae) and *Ocimum campechianum* Mill. (Lamiaceae), formely *O. micranthum*, and from inflorescences of *Ocimum carnosum* (Spreng) Link & Otto ex Benth (Lamiaceae), formely *O. selloi*, as well as their chemical composition.

MATERIALS AND METHODS

Plant material

The leaves of of *Vitex agnus-castus* and *Ocimum campechianum*, and the inflorescences of *Ocimum carnosum* were collected in August 2016 from the Horto de Plantas Medicinais Professsor Francisco José de Abreu Matos (Fortaleza, Ceará, Brazil). Plant materials were authenticated by Luiz Wilson Lima-Verde, and voucher specimens (#60102, #60105 and #60104) were deposited at the Herbário Prisco Bezerra (EAC), Departamento de Biologia, Universidade Federal do Ceará, Brazil.

Extraction of the essential oils

Fresh leaves of *V. agnus-castus* and *O. campechianum*, and fresh inflorescences of *O. carnosum* were subjected to hydrodistillation in a Cleavenger-type apparatus for 2 hours. The isolated oils, after drying over anhydrous sodium sulfate and filtration, were stored in sealed glass vials and maintained under refrigeration until further analysis. The yields (w/w) were calculated based on the fresh weight of the botanical material.

GC/MS and GC analysis of essential oils

GC analyses were performed using a GC-MS/FID (QP2010 Ultra, Shimadzu Corporation, Kyoto, Japan) equipped with an autosampler AOC-20i (Shimadzu). Separations were accomplished using a Rtx®-5MS Restek fused silica capillary column (5%-diphenyl–95%-dimethyl polysiloxane) of 30 m × 0.25 mm i.d., 0.25 mm film thickness, at a constant helium (99.999%) flow rate of 1.2 mL/min. The essential oils were dissolved in ethyl acetate (5 mg/mL) and an injection volume of 0.5 µL was employed, with a split ratio of 1:10. The oven temperature was programmed from 50°C (isothermal for 1.5 min), with an increase of 4°C/min, to 200°C, then 10°C/min to 250°C, ending with a 5 min isothermal at 250°C.

The MS and FID data were simultaneously acquired employing a Detector Splitting System; the split flow ratio was 4:1 (MS:FID). A 0.62 m x 0.15 mm i.d. restrictor tube (capillary column) was used to connect the splitter to the MS detector; a 0.74 m x 0.22 mm i.d. restrictor tube was used to connect the splitter to the FID detector. The MS data (total ion chromatogram, TIC) were acquired in the full scan mode (*m/z*

40–350) at a scan rate of 0.3 scan/s using the electron ionization (EI) with an electron energy of 70 eV. The injector temperature was 250°C and the ion-source temperature was 250°C. The FID temperature was set to 250°C, and the gas supplies for the FID were hydrogen, air, and helium at flow rates of 30, 300, and 30 mL/min, respectively. Quantification of each constituent was estimated by FID peak-area normalization (%). Compound concentrations were calculated from the GC peak areas and they were arranged in order of GC elution.

Identification of essential oils constituents

The identification of individual components of the essential oils was performed by computerized matching of the acquired mass spectra with those stored in NIST21, NIST107 and WILEY8 mass spectral library of the GC-MS data system. A mixture of hydrocarbons (C_9H_{20}–$C_{19}H_{40}$) was injected under these same conditions and identification of constituents was then performed by comparing the spectra obtained with those of the equipment data bank and by the Kovats index, calculated for each constituent as previously described (Adams 2007). Retention indices were obtained with equation proposed by van Den Dool & Kratz (1963).

Larvicidal biossay

Aliquots of the essential oils tested (12.5 to 500 µg/mL) were placed in a beaker (50 mL) and dissolved in DMSO/H_2O 1.5% (20 mL). Fifty instar III larvae of *Ae. aegypti* were delivered to each beaker. For each experiment, both positive (Temephos®) and negative (H_2O/DMSO 1.5%) control assays were carried out in parallel. After 24 hours, at room temperature, the number of dead larvae was counted and the lethal percentage calculated. For each sample, 3 independent experiments were run (Oliveira et al. 2002). Larvae of *Ae. aegypti* were collected from mosquito colonies maintained at NUVET – SESA (Núcleo de Controle de Endemias Transmissíveis por Vetor - Secretaria de Saúde do Estado do Ceará).

Cytotoxicity assay

The human tumor cell lines used were breast adenocarcinoma (MCF-7), lung carcinoma (NCI-H292), pro-myelocytic leukemia (HL-60), and cervical adenocarcinoma (HEP-2) which were obtained from the Banco de Células do Rio de Janeiro (RJ, Brazil). Cancer cells were maintained in RPMI 1640 medium or DMEN supplemented with 10% fetal bovine serum, 2 mm/L glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin at 37 °C with 5% CO_2. The cytotoxic activities of essential oils were tested against four human tumor cell lines using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT; Sigma Aldrich Co., St. Louis, MO, USA) reduction assay (Mosmann 1983). For all experiments, tumor cells were plated in 96-well plates (10^5 cells/mL for adherent cells or 3 x 10^5 cells/mL for leukemia). The essential oils dissolved in DMSO 1% were added to each well and incubated for 72 h. Control groups received the same amount of DMSO. The compound concentrations added to the cells ranged from 0.39 to 25.00 µg/mL. After 69 h of treatment, MTT (0.5 mg/mL) was added, three hours later, the MTT formazan product was dissolved in 100 µL of DMSO, and absorbance was measured at 570 nm in plate spectrophotometer (Varioskan Flask, Thermo Scientific). Doxorubicin was used as positive control. IC_{50} values and their 95% confidence intervals for two different experiments were obtained by non linear regression using Graphpad Prism version 5.0 for Windows (GraphPad Software, San Diego, California, USA).

RESULTS

Chemical analysis of the essential oils

The yields of essential oils obtained by the hydrodistillation of fresh leaves of *V. agnus-castus* and *O. campechianum*, and of fresh inflorescences of *O. carnosum* were 0.1%, 0.4% and 0.5% (w/w), respectively, in relation to the weight of the plant material. The chemical composition of the essential oils, including the retention index and the percentage relative of each constituent identified, is shown in Table I. The GC chromatograms of essential oils from the leaves of *V. agnus-castus* and *O. campechianum*, and from inflorescences of *O. carnosum* are presented in Figures 1, 2 and 3, respectively.

In the essential oil from leaves of *V. agnus-castus*, nine constituents were identified representing 100.0% of the total composition. The components of this essential oil were identified as 1,8-cineole (47.9%), terpinyl α-acetate (11.6%), sabinene (11.2%), caryophyllene oxide (9.7%), terpinen-4-ol (4.6%), (*E*)-caryophyllene (4.4%), spathulenol (4.4%), α-*epi*-cadinol (4.2%) and bicyclogermacrene (2.0%). The monoterpene and sesquiterpene fractions represent 75.3% and 24.7% of the oil, respectively.

Table I. Chemical composition of essential oils of *V. agnus-castus*, *O. campechianum* and *O. carnosum*.

Compound	RT (min)[a]	RRI exp.[b]	RRI lit.[c]	*V. agnus-castus* (%)	*O. campechianum* (%)	*O. carnosum* (%)
Sabinene	11.62	960	969	11.2	-	-
1,8-Cineole	13.83	1025	1026	47.9	2.9	2.8
Fenchone	16.07	1081	1083	-	-	2.2
Linalool	16.42	1089	1095	-	-	79.0
Camphor	18.30	1137	1146	-	-	2.2
Terpinen-4-ol	19.57	1170	1174	4.6	-	3.2
δ-Elemene	25.47	1335	1335	-	1.2	-
Terpinyl α-acetate	25.83	1344	1346	11.6	-	-
Eugenol	26.20	1355	1356	-	72.1	-
β-Elemene	27.41	1388	1389	-	6.8	-
(*E*)-Caryophyllene	28.48	1416	1417	4.4	6.4	-
α-*Trans*-Bergamotene	28.88	1429	1432	-	-	2.8
α-Humulene	29.65	1452	1452	-	1.3	-
Germacrene D	30.56	1481	1484	-	-	2.4
Bicyclogermacrene	31.07	1496	1500	2.0	5.2	-
Elimicine	32.75	1547	1555	-	4.1	-
Spathulenol	33.72	1576	1577	4.4	-	-
Caryophyllene oxide	33.92	1582	1582	9.7	-	-
α-*Epi*-Cadinol	35.61	1647	1638	4.2	-	5.4
Monoterpenes				**75.3**	**2.9**	**89.4**
Sesquiterpenes				**24.7**	**20.9**	**10.6**
Phenylpropanoids				**-**	**76.2**	**-**
Total identified				**100.0**	**100.0**	**100.0**

[a]**Retention time;** [b]**Relative retention index calculated against *n*-alkanes (C_9H_{20}–$C_{19}H_{40}$) applying the Van den Dool & Kratz (1963) equation;** [c]**Relative retention index from the literature (Adams, 2007).**

Eight compounds, representing 100% of the essential oil from leaves of *O. campechianum* have been identified. Eugenol (72.1%), β-elemene (6.8%), (*E*)-caryophyllene (6.4%), bicyclogermacrene (5.2%), elimicine (4.1%), 1,8-cineole (2.9%), α-humulene (1.3%) and δ-elemene (1.2%) were the components. Phenylpropanoids (76.2%), sesquiterpenes (20.9%) and monoterpenes (2.9%) were found in this oil.

In the essential oil obtained from inflorescences of *O. carnosum*, eight constituents were identified. The components were linalool (79.0%), α-*epi*-cadinol (5.4%), terpinen-4-ol (3.2%), 1,8-cineole (2.8%), germacrene D (2.4%), α-*trans*-bergamotene (2.8%), fenchone (2.2%) and camphor (2.2%). This essential oil consists of 10.6% of sesquiterpenes and 89.4% of monoterpenes.

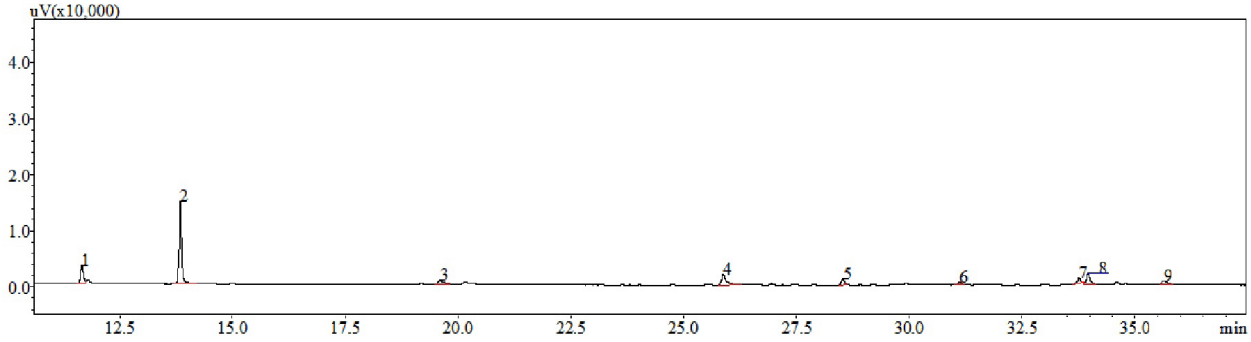

Figure 1. Chromatogram (CG-DIC) of essential oil from leaves of ***Vitex agnus-castus.***

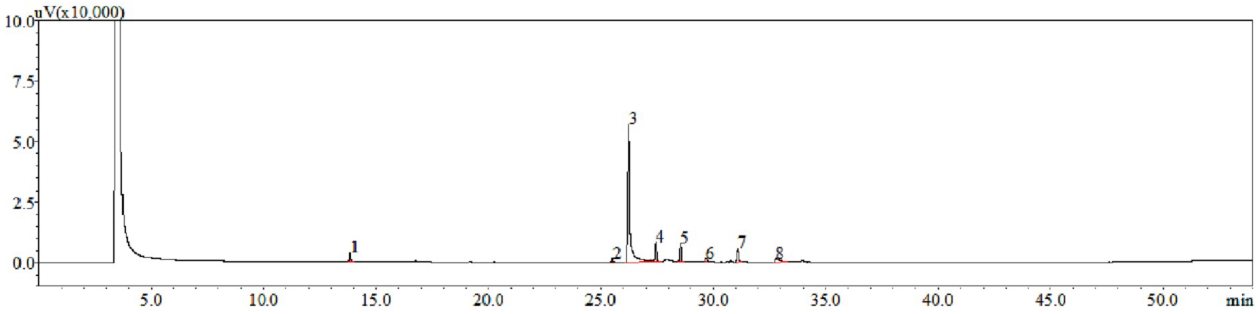

Figure 2. Chromatogram (CG-DIC) of essential oil from leaves of ***Ocimum campechianum.***

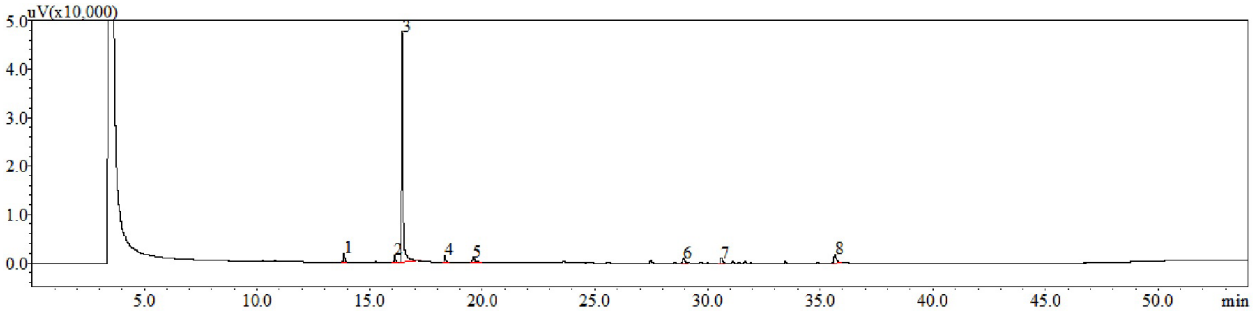

Figure 3. Chromatogram (CG-DIC) of essential oil from inflorescences of ***Ocimum carnosum.***

Larvicidal activity

Essential oils from leaves of *V. agnus-castus* and *O. campechianum*, and from inflorescences of *O. carnosum* were screened for their activity against instar III larvae of *Ae. aegypti*. The mortality percentages were calculated after 24 h. The larvicidal effects of tested essential oils against instar III *Ae. aegypti* larvae are shown in Table II. In our experiments, the mortality of larvae ranged from 100% to 0%, when *Ae. aegypti* larvae were treated with the tested essential oils (Table II). *O,O'*-(Thiodi-4,1-phenylene)bis(*O,O*-dimethyl phosphorothioate (Temephos®) was used as a positive control (LC_{50} 1.4 ± 0.2 µg/mL).

Additional data on the toxicity of essential oils have been obtained by calculation of their LC_{50} values and, thus the essential oils obtained from leaves of *V. agnus-castus* and *O. campechianum* and from inflorescences of *O. carnosum* showed LC_{50} values of 97.55 ± 0.35, 81.45 ± 0.35 and 109.49 ± 0.35 µg/mL, respectively.

Cytotoxic activity

The essential oils from *V. agnus-castus*, *O. campechianum* and *O. carnosum* were submitted to the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay (Mosmann 1983) for the evaluation of their cytotoxic effects on breast adenocarcinoma (MCF-7), lung carcinoma (NCI-H292), pro-myelocytic leukemia (HL-60), and cervical adenocarcinoma (HEP-2) human cell lines (Table III). Doxorubicin was used as the positive control. The essential oils from *V. agnus-castus*, *O. campechianum*, *O. carnosum* were more active against pro-myelocytic leukemia (HL-60) cell lines with IC_{50} values of 3.8, 7.6, and 13.2 µg/mL, respectively (Table III).

Table II. Larval mortality (%) of essential oils against third-instar of *Aedes aegypti* larvae.

Concn (µg/mL)	Average (%) of dead larvae after 24 h[a]		
	Vitex agnus-castus	***Ocimum campechianum***	***Ocimum carnosum***
500	100	100	100
250	100	100	100
100	52.67	69.33	23.33
50	5.33	12.57	0.67
25	0	0	0
12.5	0	0	0

[a] **The results were means of three independent experiments.**

Table III. Cytotoxic activity of essential oils.

Essential oil and positive control	IC_{50} (µg/mL) (95% confidence intervals)[a]			
	MCF-7	**NCI-H292**	**HL-60**	**HEP-2**
Vitex agnus-castus	32.4 (26.4-39.7)	46.5 (40.1-53.8)	3.8 (1.7-8.2)	41.7 (29.9-58.2)
Ocimum campechianum	20.3 (12.1-31.9)	37.2 (33.4-41.5)	7.6 (4.3-13.6)	31.4 (23.8-41.5)
Ocimum carnosum	25.5 (17.8-36.4)	>50	13.2 (8.1-21.7)	20.1 (14.2-23.8)
Doxorubicin	0.30 (0.19-0.53)	0.30 (0.10-0.40)	0.03 (0.01-0.03)	0.70 (0.30-1.70)

[a] **The results were means of two independent experiments.**

DISCUSSION

Essential oils are obtained from aromatic plants, mainly by steam distillation or hydrodistillation. They are considered promising in the control of mosquitoes as *Ae. aegypti* because consist of a mixture of volatile substances with a variety of functional groups that can be toxic to insects (Bakkali et al. 2008, Dias & Moraes 2014). In the larvicidal activity of essential oils, the lipophilicity of their chemical constituents is associated with the percutaneous permeation of essential oils (El-Kattan et al. 2001).

The large abundance of monoterpenoid compounds, mainly 1,8-cineole, in the leaf essential oil of *V. agnus-castus* is in accordance with previous findings (Borges et al. 2012, Dervishi-Shengjergji et al. 2014, Neves & Da Camara 2016). It is important to note that only 9 constituents were identified in this essential oil, and this number is similar to that reported for other sample collected in the northeastern Brazil, which presented 11 constituents (Borges et al. 2012). Monoterpenes have been reported to display larvicidal and insecticidal activities (Santos et al. 2011, Michaelakis et al. 2014, Liu et al. 2015, Polatoglu et al. 2017). The constituents 1,8-cineole (Araújo et al. 2003, Lucia et al. 2007, Cheng et al. 2009), terpinyl α-acetate (Cheng et al. 2009, Pandey et al. 2013), and sabinene (Govindarajan 2010, Cheng et al. 2013) have shown larvicidal or insecticidal activity against *Ae. aegypti*, and these constituents were detected in the essential oil from leaves of *V. agnus-castus*.

The presence of the phenylpropanoid eugenol in the essential oil from leaves of *O. campechianum*, as a major chemical constituent, is in accordance with previous reports (Sacchetti et al. 2004, Silva et al. 2004, Trevisan et al. 2006, Vieira et al. 2014). Earlier investigations into the essential oils of this species growing in the same place, under same conditions, have found similar chemical composition (Silva et al. 2004, Trevisan et al. 2006, Vieira et al. 2014). It is generally admitted that the major constituents determine the biological properties of the essential oils (Riella et al. 2012, Dias & Moraes 2014). In this way, the larvicidal effect of this essential oil can be attributed to eugenol, which has been reported to exhibit activity against *Ae. aegypti* larvae (Walıwıtıya et al. 2009, Barbosa et al. 2012, Medeiros et al. 2013, Dias & Moraes 2014, Fayemiwo et al. 2014).

In the present study, the major constituent identified in the essential oil from inflorescences of *O. carnosum* was linalool (79.0%), whereas the literature reports methyl chavicol (92.5%) and methyl eugenol (66.2%) from two different accessions (Martins et al. 1997), *trans*-anethole (41.3%) and methyl chavicol (27.1%) (Moraes et al. 2002), as the major constituents. The variations in the chemical composition may be related with chemotypes for the same species or as a result of factors such as temperature, soil type, climate, and developmental and physiological differences (Nascimento et al. 2011, Fayemiwo et al. 2014). The essential oil of *O. carnosum*, which has linalool as the major constituent, exhibited larvicidal activity, with LC_{50} value of 109.49 ± 0.35 µg/mL. In previous studies, Jantan et al. (2005), Pandey et al. (2013) and Fujiwara et al. (2017) evaluated the larvicidal activity of linalool against *Ae. aegypti*, and observed LC_{50} values of 157.4, 242.6 and 275.2 µg/mL, respectively. Therefore, it is possible that other constituents of the essential oil work synergistically with linalool.

Among the essential oils evaluated against *Ae. aegypti* larvae, the leaf essential oil of *O. campechianum* was the most active with LC_{50} value of 81.45 ± 0.35 µg/mL, and generally, all phenylpropanoid-rich essential oils exhibited larvicidal activity (Dıas & Moraes 2014).

The cytotoxic activity of 1,8-cineole (Moteki et al. 2002, Sampath et al. 2017), eugenol (Rajput et al. 2017, Fangjun & Zhijia 2018), and linalool (Cheng et al. 2017, Aprotosoaie et al. 2014), major constituents in *V. Agnus-castus*, *O. campechianum* and *O. carnosum* essential oils, respectively, has been shown in previous studies. Therefore, it is possible that these constituents of the essential oils work synergistically to produce the cytotoxic activity of tested essential oils.

CONCLUSIONS

The results obtained show that the essential oils, especially that obtained from leaves of *O. campechiamum* could be considered as natural larvicidal agents. With respect to cytotoxic activity, pro-myelocytic leukemia cells lines (HL-60) were found to be the most sensitive to all the essential oils tested than the others. These findings indicate that that the differences in the activities of the essential oils were related to their chemical composition.

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Lara P. Ricarte, Gabrieli P. Bezerra and Nirla R. Romero contributed to plants collection and confection of herbarium, running the laboratory work. Lara P. Ricarte, Telma L.G. Lemos, Péricles B. Alves and Marcelo B. dos Santos contributed in the chemical analysis of the essential oils. Horlando C. da Silva, Gardenia C. G. Militão and Thiago D. S. Silva contributed to biological assays. Gilvandete M. P. Santiago designed the study, supervised the laboratory work and wrote the manuscript. Angela M. C. Arriaga and Raimundo Braz-Filho are responsible for reviewing the article. All the authors have read the final manuscript and approved the submission.