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Ritmo Circadiano e Atividade Larvicida contra *Aedes aegypti* de Óleos Essenciais de *Croton piauhiensis*

Resumo: *Croton piauhiensis* Müll. Arg., popularmente conhecido como velame, é uma espécie restrita do bioma Caatinga. Neste contexto, este trabalho tem como objetivo estudar pela primeira vez o ciclo circadiano e a atividade larvicida contra o *Aedes aegypti* dos óleos essenciais de *C. piauhiensis*. A composição química dos óleos essenciais de folhas obtidas por hidrodestilação foi analisada e identificada por GC-MS e GC-FID. De acordo com os resultados, o estudo circadiano mostrou diferenças na composição química dos óleos extraídos em diferentes horas do dia das folhas de *C. piauhiensis*. Os principais componentes dos óleos essenciais das folhas de *C. piauhiensis* são obtidos às 8h, 12h e 17h, foram β-cariofileno 21,58, 34,69 e 21,01 %, D-limoneno 13,47, 13,75 e 16,35, γ-terpineno 10,08, 8,00 e 9,60 %, germacreno D 9,56, 10,42 e 8,71 %, respectivamente. O teor de sesquiterpenos foi de 52,59 % e 67,29 % às 8h e 12h, respectivamente. Por outro lado, às 17h houve maior predominância dos monoterpenos (50,77 %). Em relação à atividade larvicida, os óleos essenciais de *C. piauhiensis* apresentaram atividade larvicida com CL_{50} = 336,8 μg / mL (óleo extraído às 8:00 h), CL_{50} = 283,9 μg / mL (óleo extraído a partir das 12:00 h) e CL_{50} = 252,5 μg / ml (óleo extraído às 17:00 h).

Palavras-chave: *Croton piauhiensis*; óleos essenciais; ciclo circadiano.

Abstract

Croton piauhiensis, popularly known as velame, is a restricted species of Caatinga biome. In this context, this work aims to study for the first time the circadian cycle and larvicidal activity against *Aedes aegypti* of the essential oils from *C. piauhiensis*. The chemical composition of the essential oils from leaves obtained by hydrodistillation was analyzed and identified by GC-MS and GC-FID. According to the results, the circadian study showed differences in the chemical composition of oils extracted from *C. piauhiensis* leaves collected at different hours of the day. The major components of essential oils from *C. piauhiensis* collected at 8, 12 and 17 h, were β-caryophyllene 21.58, 34.69 and 21.01 %, D-limonene 13.47, 13.75 and 16.35, γ-terpinene 10.08, 8.00 and 9.60 %, germacrene D 9.56, 10.42 and 8.71 %, respectively. Sesquiterpenes contents were 52.59 % and 67.29 % at 8 and 12 h, respectively. On the other hand, at in the oil collected 17 h there was a greater predominance of the monoterpenes (50.77 %). Regarding the larvicidal activity, the essential oils of *C. piauhiensis* showed larvicidal activity with LC_{50} = 336.8 μg / mL (oil extracted at 8:00 h), LC_{50} = 283.9 μg/mL (oil extracted at 12:00 h) and LC_{50} = 252.5 μg /ml (oil extracted at 17:00 h).

Keywords: *Croton piauhiensis*; essential oils; circadian rhythm.

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Circadian Rhythm and Larvicidal Activity Against *Aedes aegypti* of Essential Oils from *Croton piauhiensis*

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1. Introduction

Plants are sources of several bioactive secondary metabolites, and natural products from plants are very interesting and promising, mainly due to their potential applications in the food and pharmaceutical industries.[1-3] Essential oils (EOs) are defined as a complex mixture of volatile substances, which can be extracted from different parts of the plant such as flowers, fruits, seeds, leaves, wood, bark and roots.[4] In addition, several biological activities have been attributed to EOs including antiviral,[5,6] insecticidal,[7] antiparasitic,[8,9] antimicrobial and antioxidant.[10-12]

Dengue, Zika and Chikumgunya are arboviruses with the highest circulation in Brazil, they are characterized by a group of viral diseases, transmitted by vectors, which can be transmitted to humans and other animals through the bite of *Aedes aegypti*. The World Health Organization (WHO) recognized these as a global public health problem and estimates that 50 to 100 million cases of infection occur worldwide each year.[13] The use of organophosphate insecticides for vector control can result in serious environmental problems like insecticide resistance and environmental pollution.[14] In view of the serious epidemiological picture reported and considering the absence of a specific treatment, it is essential to identify EOs that have repellent, larvicidal and insecticidal properties in the control of these arboviruses.[15]

Croton (Euphorbiaceae) is the second largest genus in its family, with approximately 1.300 species distributed throughout tropical and subtropical regions. Some species of the genus *Croton* have been used in folk medicine for the treatment and cure of some diseases.[16] Furthermore, several studies have reported the chemical characterization and biological activities of EOs extracted from *Croton* species.[17-21]

In recent years, the search for efficient natural compounds with larvicidal activity against *A. aegypti* and low environmental toxicity has increased, thus EOs of *Croton* species are outstanding candidates, since they are in some cases, they are readily available, and economically viable. In fact, the larvicidal activity of EOs extracted from *C. zehntneri*, *C. jacobinensis*, *C. argyrophylloides*, *C. sonderianus*, *C. nepetaefolius* and *C regelianus* have been previously reported. [22-25]

Croton piauhiensis (Figure 1) is an endemic species in Northeastern Brazil, found frequently in the Caatinga biome and popularly known as "velame" and "marmeleiro". There are no reports on the chemical composition and biological activities of *C. piauhiensis* essential oil. In this context, the present work aimed to evaluate for the first time the influence of the circadian cycle and larvicidal activity against *A. aegypti* of the essential oils from leaves of *C. piauhiensis*.

Figure 1. *C. piauhiensis*

2. Materials and Methods

2.1. Plant material

C. piauhiensis leaves were collected in Sobral, Ceará, Brazil (03° 36' 44'' S 40° 18' 37'' W). Plant authentication was performed by Professor Daniela Santos Carneiro-Torres, and a voucher specimen was deposited at the Universidade Estadual de Feira de Santana (HUEFS) with the identification number #14989.

2.2. Extraction of the essential oils

The fresh leaves of *C. piauhiensis* were subjected to hydrodistillation in a Clevenger-type apparatus for 2 hours. After being filtered and dried over anhydrous sodium sulfate, the isolated oils were stored in sealed glass vials, which were maintained under refrigeration at 4 °C until GC- MS and GC-FID analysis.

2.3. Gas Chromatography- Flame Ionization Detection

GC-FID for the quantitative analysis was carried out on a Shimadzu GC-17A gas chromatograph using a dimethylpolysiloxane DB-5 fused silica capillary column (30 mm x 0.25 mm, film thickness 0.25 m). H_2 was used as the carrier gas at a flow rate of 1 mL/min and 30 psi inlet pressure; split, 1:30; temperature program: 35-180 °C at 4 °C/min, then heated at a rate of 17 °C/min to 280 °C and held isothermal for 10 min; injector temperature, 250 °C; detector used FID, detector temperature, 250 °C.

2.4. Gas Chromatography-Mass Spectrometry

GC-MS for the analysis of the volatile constituents was carried out on a Hewlett-Packard Model 5971 GC/MS using a non-polar DB-5 fused silica capillary column (30 mm x 0.25 mm i.d., 0.25m film thickness); carrier gas helium, flow rate 1 mL/min and with split ratio 1:1. The injector temperature and detector temperature were 250 °C and 200 °C, respectively. The column temperature was programmed from 35 C to 180 °C at 4 °C/min and then 180 C to 250 °C at 10 °C/min. Mass spectra were recorded from 30 - 450 m/z. Individual components were identified by matching their 70 eV mass spectra with those of the spectrometer data base using the Wiley L-built library MS searches using retention indices as a preselection routine, as well as by visual comparison of the fragmentation pattern with those reported in the literature.[26]

2.5. Larvicidal bioassay

Essential oils were placed in beakers and dissolved in 20 mL H_2O/DMSO 1.5 % (v/v) at concentrations of 50-500 µg/mL, followed by the addition of 50 larvae at the third-instar. For each experiment, both positive (Temephos® at 3.22 µg/mL) and negative (distilled water containing 1.5 % DMSO) control assays were carried out. Mortality was recorded after 24 h of exposure, during which no nutritional supplement was added. The experiments were carried out at 28 ± 2 °C. Each test was performed in triplicate. Data were evaluated through regression analysis. From the regression line, the LC_{50} values were read representing the lethal concentration for 50 % larval mortality of *A. aegypti*. The bioassays were performed at the Laboratório de Entomologia, Núcleo de Endemias, Secretaria de Saúde do Estado do Ceará, Brazil.[27]

2.6. Statistical analysis

The LC_{50} value of essential oil from leaves of *C. piauhiensis* was calculated using the probit analysis of the mortality data derived from bioassays.[28]

3. Results and Discussion

The EOs extracted from the leaves of *C. piauhiensis* at 8, 12 and 17 h were analyzed by GC/MS and GC/FID (Table 1). A total of 28 constituents (97.68 %) were identified in the extracted essential oil at 8 h, being 13 monoterpenes (44.86 %) and 15 sesquiterpenes (55.59 %). For the essential oil extracted at 12 h, 21 constituents (97.65 %) were identified, being 10 monoterpenes (32.47 %) and 11 sesquiterpenes (67.29 %), whereas in the essential oil extracted at 17 h, 22 constituents (98.74 %) were identified, being 10 monoterpenes (50.77 %) and 12 sesquiterpenes (47.96 %).

The EOs obtained at 12 h showed a greater abundance of sesquiterpenes. In its identified composition, 46.43 % corresponds to thirteen monoterpenes, three oxygenates and ten non-oxygenated, 53.57 % correspond to fifteen sesquiterpenes, nine non-oxygenated and six oxygenated. The major components of essential oils from *C. piauhiensis* at 8, 12 and 17 h were β-caryophyllene 21.58, 34.69 and 21.01 %, D-limonene 13.47, 13.75 and 16.35, γ-terpinene 10.08, 8.00 and 9.60 %, Germacrene D 9.56, 10.42 and 8.71 %, respectively (Figure 2).

It is observed that the harvesting time influenced expressively the terpenic composition of the EOs, since there are variations in the percentage of monoterpenes and sesquiterpenes throughout the three evaluated schedules. At 8 h, the percentage of monoterpenes and sesquiterpenes were 44.89 % and 52.59 %, respectively. This result was different from that obtained in the 12 h, for the percentages of monoterpenes (32.47 %) and sesquiterpenes (67.29 %). At that time, the predominance of sesquiterpene compounds, which are less volatile than monoterpenes, can be attributed to the high ambient temperatures that are reached at this time (12h), when compared to the other collection schedules studied. At the time of 17 h, the percentage of monoterpenes (50.77 %) was higher than that of sesquiterpenes (47.96 %).

The chemical composition of EOS from *C. piauhiensis* showed a greater abundance of monoterpenes and sesquiterpenes. Similar results were achieved by different studies with the same genus, showing also the predominance of monoterpenes and sesquiterpenes.[29,30] Moreover, the major constituents of the essential from *C. piauhiensis* were β-caryophyllene, D-limonene, germacrene D and γ-terpinene. In fact, these components appear in other studies as main constituents of essential oils from different *Croton* species. Moreover, in the essential oils from some *Croton* species, such as *C. rhamnifolioides*, *C. conduplicatus*, *C. decaryi* and *C. geayi*, β-caryophyllene is the most abundant constituent.[31,32]

The circadian variation in EOs from leaves of *C. piauhiensis* was affected by climatic conditions, resulting in the production of different constituents in different proportions. The factors, such as temperature, solar radiation intensity, rainfall index, *etc.*, act with varying degrees of intensity, mediating the quantity and nature of the substances produced.[33] The influence of edaphoclimatic factors can be observed in EOs of *Ocimum gratissimum*, whose eugenol content is about 11 % at 12 and 98 % at 5 h.[34]

Larvicidal activity of EOs of the some species from genus *Croton* has been previously reported, for instance, EOs from leaves, stalks and inflorescences of *C. zehntneri* and *C. jacobinensis* showed LC_{50} values of 56.2, 51.3, 57.5 and 79.3, 117.2, 65.8 μg/mL, respectively, were tested at different concentrations against *A. aegypti*.[22,23] EOs from aerial parts of *C. argyrophylloides*, *C. sonderianus* and *C. nepetaefolius* showed LC_{50} values of 94.6, 54.5 and 66.4 μg/mL, respectively,[24] and whereas EOs from leaves of *C. regelianus* growing in two different sites at Ceará State (Brazil) showed LC_{50} values of 24.22 and 66.74 μg/mL.[25]

The larvicidal activity from leaves EOs of *C. piauhiensis* were evaluated against *A. aegypti* using Temephos® (*O,O*'-(thiodi-4,1-phenylene) bis (*O,O*-dimethyl phosphorothioate) as positive control. The mortality percentages were calculated after 24 h. The larvicidal effects of these essential oils are shown in Table 2. The essential oils obtained at 8, 12 and 17 h showed LC_{50} values of of 336.8, 283.9 and 252.5 μg/mL, respectively. Therefore, the different activities of the essential oils can be attributed to the variation of their chemical compositions.

Essential oils from the leaves of *C. piauhiensis* demonstrated larvicidal activity against *Aedes aegypti*, which can be explained by a possible relationship between larvicidal activity and the presence of monoterpenes (α-pinene, sabinene, β-pinene, myrcene, α-terpinene, D-limonene and γ-terpinene, terpinen-4-ol) and sesquiterpenes (*β*-caryophyllene and germacrene D) which have been reported to be active against *A. aegypti* and can serve to increase the transmembrane absorption of lipophilic drugs, which can kill larvae of *A. aegypti* and mediate synergistic effects.[35-38]

Table 1. Chemical composition of essential oil from leaves of *C. piauhiensis*

Compounds	RI[a]	RI[b]	%		
			8.00 h	**12.00 h**	**17.00 h**
α-Thujene	933	924	0.62	0.45	0.59
α-Pinene	941	932	1.22	1.10	2.37
Sabinene	979	969	3.41	1.52	3.61
β-Pinene	984	974	0.24	1.48	0.30
Myrcene	994	988	3.34	0.45	3.89
α-Terpinene	1023	1017	0.57		0.53
p-Cymene	1031	1024	1.31	0.91	1.37
D-Limonene	1034	1029	13.47	13.75	16.35
Eucalyptol	1037	1031	4.92	3.14	6.88
γ-Terpinene	1064	1059	10.08	8.00	9.60
Terpinolene	1093	1088	1.35	1.67	1.32
Linalool	1104	1096	2.33		2.41
Terpinen-4-ol	1183	1177	2.03		1.55
δ-Elemene	1341	1338	0.62		0.71
α-Copaene	1379	1376	0.64	0.65	0.59
β-Elemene	1394	1390	1.63	1.40	1.96
β-Caryophyllene	1423	1419	21.58	34.69	21.01
α-Caryophyllene	1457	1454	2.54	4.30	2.46
Germacrene D	1484	1485	9.56	10.42	8.71
Bicyclogermacrene	1498	1500	6.62	8.49	6.94
γ-Cadinene	1517	1513	0.55		
δ-Cadinene	1526	1523	1.45	1.50	1.17
Spathulenol	1581	1578	0.90		
Caryophyllene oxide	1586	1583	1.29	1.84	0.83
1-*epi*-Cubenol	1632	1628	0.37		
α-*epi*-Muurolol	1646	1642	3.03	1.84	1.39
δ-Cadinol	1650	1646	0.79	1.15	1.56
α-Cadinol	1659	1654	1.02	1.01	0.63
Total			97.48	97.65	98.74

[a]Retention index on DB-5 column; [b]Literature retention index

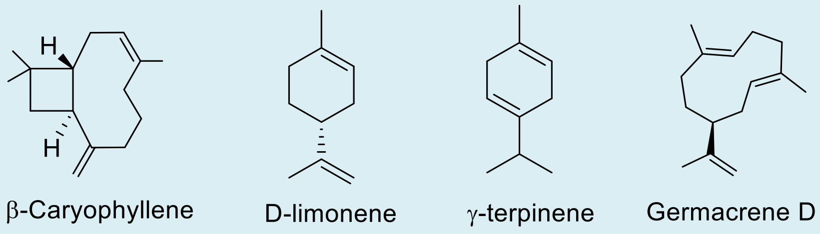

Figure 2. The main constituents of the essential oil from the leaves of *C. piauhiensis*

Table 2. Larval mortality (%) and LC_{50} values of essential oils against third-instar of *Aedes aegypti* larvae

Essential oil	Concentration (µg/mL)	Average (%) of dead larvae after 24 h (%)	LC_{50} (µg/mL)
8.00 h	500	98.7	336.8
	250	4.0	
	100	0.0	
	50	0.0	
12.00 h	500	90.8	283.9
	250	38.0	
	100	8.7	
	50	0.0	
17.00 h	500	99.46	252.5
	250	48.7	
	100	28.00	
	50	8.7	

4. Conclusion

The circadian study of essential oils from *C. piauhiensis* allowed us to conclude that the variations observed in the concentration of the chemical constituents can be attributed to environmental conditions. The major components of essential oils from *C. piauhiensis* were β-caryophyllene, D-limonene, γ-terpinene and germacrene D. Additionally, essential oils from the leaves of *C. piauhiensis* demonstrated larvicidal activity against *Aedes aegypti*, which can be explained by a possible relationship between larvicidal activity and the presence of monoterpenes and sesquiterpenes since these substances can serve to increase the transmembrane absorption of lipophilic drugs, which can kill larvae of *A. aegypti* and mediate synergistic effects.

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