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First Report on the Chemical Composition, Antioxidant Capacity, and Preliminary Toxicity to *Artemia salina* L. of *Croton campinarensis* Secco, A. Rosário & PE Berry (Euphorbiaceae) Essential Oil, and In Silico Study

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Abstract: *Croton campinarensis* Secco, A. Rosário & PE Berry is an aromatic species recently discovered in the Amazon region. This study first reports the chemical profile, antioxidant capacity, and preliminary toxicity to *A. salina* Leach of the essential oil (EO) of this species. The phytochemical profile of the essential oil was analyzed by gas chromatography (GC/MS) and (GC-FID). The antioxidant capacity of the EO was measured by its inhibition of $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ radicals. Molecular modeling was used to evaluate the mode of interaction of the major compounds with acetylcholinesterase (AChE). The results indicate that the EO yield was 0.24%, and germacrene D (26.95%), bicyclogermacrene (17.08%), (*E*)-caryophyllene (17.06%), and δ-elemene (7.59%) were the major compounds of the EO sample. The EO showed a TEAC of 0.55 ± 0.04 $mM \cdot L^{-1}$ for the reduction of the $ABTS^{\bullet+}$ radical and 1.88 ± 0.08 $mM \cdot L^{-1}$ for the reduction of the $DPPH^{\bullet}$ radical. Regarding preliminary toxicity, the EO was classified as toxic in the bioassay with *A. salina* (LC_{50} = 20.84 ± 4.84 $\mu g \cdot mL^{-1}$). Through molecular docking, it was found that the majority of the EO components were able to interact with the binding pocket of AChE, a molecular target related to toxicity evaluated in *A. salina* models; the main interactions were van der Waals and π-alkyl interactions.

Keywords: Amazon; new species; natural products; bioactive compounds; molecular modeling

1. Introduction

Natural products, in particular volatile oils isolated from aromatic plants, have been the subject of several studies over the years. This may be related to their complex chemical compositions, which may include a series of classes of chemical compounds such as monoterpenes, sesquiterpenes, hydrocarbons, oxygenated mono- and sesquiterpenes, and phenylpropanoids [1–4]. In addition, this diverse chemical composition may be related to potential activities, such as antioxidant [5–7]. Amazonian flora, for example, include several aromatic plant species that produce EOs [8,9] that can serve as inputs for various sectors of the chemical, pharmaceutical, cosmetic, and food industries; these potential applications show promise in generating development in the region [4,10–12]. Among

Amazonian species that produce EOs, those belonging to the family Euphorbiaceae stand out, especially species of the genus *Croton* [13].

The *Croton* genus includes a variety of over 1200 species with a widespread global distribution in both the tropics and subtropics, especially in arid and semiarid zones [14]. In Brazil, 300 species are found, of which 230 are considered endemic. In the Amazon region, 61 species have been recorded [15]. *Croton* species have shrub characteristics, can resprout in rainy seasons, and grow widely, especially in deforested areas [16].

Several species of *Croton* have chemical compounds used for medicinal purposes, mainly as anti-inflammatory, antihypertensive, antifungal, antimicrobial, antidiabetic, antioxidant, antinociceptive, and antitumor agents [16]. In traditional medicine, the leaves of species of this genus are used to treat gastrointestinal disorders, rheumatism, migraine, diabetes, cholesterol level, inflammatory diseases, and bronchitis [17–19]. The EOs of species of the genus *Croton* are characterized by different chemical classes of compounds, with a predominance of terpenoids and phenylpropanoids [20]. Compounds such as limonene, (*E*)-caryophyllene, spathulenol, bicyclogermacrene, germacrene D, (*E*)-anathole, and estragol are common components of EOs of *Croton* species [21–26].

The EOs of *Croton* species have also been widely studied for the discovery of new natural antioxidants [27–31]. Antioxidant substances can inhibit free radicals [32,33], which may be responsible for the damage caused by oxidative stress related to various diseases, such as Alzheimer's disease, Parkinson's disease, cancer, and diabetes [34]. The use of natural antioxidant compounds rather than synthetic antioxidants is currently being widely explored, as the former pose lower human health risks, especially those related to high toxicity and the triggering of new diseases caused by synthetic products [35–37].

When evaluating the toxicity of EOs, preliminary tests are performed to ensure their safety for humans [38,39]. Preliminary toxicity tests on *A. salina* allow an initial response to the potential toxicity of an extract or isolated substance; this is due to the sensitivity similar to that of human cells that the microcrustacean presents. [40]. The EOs of some species of the genus *Croton* have moderate or high toxicity against *A. salina*, which is directly related to the high sesquiterpene content in their chemical composition [41–44].

This bioassay is also important due to the biochemical activity of the enzyme acetylcholinesterase (AChE), which mediates the larval mortality of *A. salina* when individuals come into contact with EO within 24 h; the number of deaths of microcrustaceans is counted, which indicates a potential biological activity of the essential oil [45]. This enzyme is also directly related to the behavior and physiology of *A. salina*, and its inhibition may cause deleterious effects in individuals [46].

Croton campinarensis Secco, A. Rosário & PE Berry is a recently discovered species recorded for the first time in 2012 [47]. The species is listed only in the state of Pará, located in the Brazilian Amazon [15]. Because it is a recently known species, there are no records in the literature related to the chemical composition and antioxidant and biological properties of its EO. As a result, the present study first reports the yield, chemical composition, antioxidant profile, and preliminary toxicity of the EO of dry leaves of *C. campinarensis*, aiming to contribute to the phytochemical knowledge of aromatic plants of the genus *Croton* from the Amazon region.

2. Materials and Methods

2.1. Collection and Processing of Botanical Material

Leaves of *C. campinarensis* were collected in the locality of Campina do Guajará, municipality of Bujaru (Latitude: 1°31′15″ S, Longitude: 48°2′37″ W), microregion of Castanhal, Pará State, Brazil, in July 2017. The sample was identified and deposited in the herbarium of the Museu Paraense Emílio Goeldi, Belém, Pará, with registration number MG167619.

2.2. Distillation of Essential Oil

The processed botanical material was subjected to hydrodistillation to obtain EO, using a modified Clevenger apparatus for 3 h. After distillation, the EO was centrifuged and dehydrated with anhydrous sodium sulfate (Na_2SO_4). Then, it was stored and preserved in a freezer. The EO yield was calculated on a moisture-free basis [45].

2.3. Analysis of the Chemical Composition of the Essential Oil

The analysis of the phytochemical profile of the essential oil of *C. campinarensis* was carried out following the same protocols of our research group, as well as the brand and model of the equipment [33,48–50]. Masses (GC-MS) and quantification were performed by gas chromatography with a flame ionization detector (GC-FID). The identifications in the GC/MS were performed based on the calculated retention index [51] and compared with the literature [52].

2.4. Determination of the Trolox Equivalent Antioxidant Capacity (TEAC) of the Essential Oil

2.4.1. DPPH Method

This method was performed to analyze the potential of EO of *C. campinarensis* to inhibit the 1,1-diphenyl-2-picrylhydrazyl ($DPPH^{\bullet}$) radical, a violet chromophore, resulting in the formation of the hydrogenated DPPH product, which is yellow or colorless [53]. Description of the method can be found in [54].

2.4.2. ABTS Method

This method was performed to analyze the potential of *C. campinarensis* EO to inhibit the 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS; Sigma-Aldrich; A1888, São Paulo, Brazil) radical, according to modification by Re et al. [55] of the experimental method proposed by Miller et al. [56]. Description of the method can be found in [54].

2.5. Determination of Preliminary Toxicity against Artemia salina Leach

For toxicity tests on *A. salina*, the essential oil was prepared at concentrations ranging from 1–100 $\mu g \cdot mL^{-1}$, according to methods described by [45]. A total of ten *A. salina* larvae were added to each test flask with the aid of automatic micropipettes. In the control group and the positive group with lapachol, the same solvent was used for the samples and larvae, under the same conditions as the bioassay. The counting of *A. salina* was carried out after a period of 24 h at each concentration used and the IC50 was calculated, with the experiments being carried out in triplicate ($n = 3$).

2.6. Statistical Analysis

In the experimental tests, with the exception of the analysis of the chemical composition, the statistical Student's *t*-test was applied, and a significance level of 5% ($p \leq 0.05$) was considered.

2.7. Molecular Docking

For the molecular docking studies, data on the major compounds germacrene D (26.95%), bicyclogermacrene (17.98%), (*E*)-caryophyllene (17.60%), γ-terpinene (8.99%), and δ-elemene (7.59%) were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/, accessed on 1 October 2022). Then, their structures were optimized with B3LYP/6-31G* using Gaussian 09 software (Gaussian, Inc., Wallingford, England) [57–60].

Molecular interactions were performed with the majority compounds and AChE in Molegro Virtual Docker (MVD) 5.5 software (Molexus IVS, Odder, Denmark) [61–64]; the structure of the protein used in the molecular modeling study can be obtained from the Protein Data Bank (https://www.rcsb.org/, accessed on 1 September 2022), using the ID code 4M0E [65]. The MolDock Score (GRID) was carried out as described by [45].

3. Results and Discussion

3.1. Yield and Chemical Composition of the Essential Oil

The EO yield for the studied sample was 0.24%, we can observe in Table 1. There are no records in the literature regarding the yield and volatile composition of the EO of *C. campinarensis*. However, the yield found in the present study is lower than that reported by Turiel et al. [66] for four *Croton* species from the Amazon (0.50% ± 1.10%). Another notable finding is the high concentration of sesquiterpene hydrocarbons found in both the present sample and the species analyzed by Turiel et al. [66], which had levels between 55.30% and 83.00%.

Table 1. Main chemical constituents and EO yield of *C. campinarensis*.

	Yield (%)		**0.24**
RI_L	**RI_C**	**Chemical Constituents**	**Area (%)**
1014 [a]	1017	α-terpinene	0.31
1020 [a]	1024	*p*-cymene	0.49
1054 [a]	1059	γ-terpinene	8.99
1335 [a]	1339	δ-elemene	7.59
1374 [a]	1378	α-copaene	0.34
1387 [a]	1387	β-bourbonene	0.45
1389 [a]	1394	β-elemene	3.56
1409 [a]	1412	α-gurjunene	0.48
1417 [a]	1423	(*E*)-caryophyllene	17.60
1430 [a]	1431	β-copaene	1.37
1434 [a]	1434	γ-elemene	0.43
1432 [a]	1437	α-*trans*-bergamotene	1.03
1447 [b]	1446	isogermacrene D	0.60
1452 [a]	1456	α-humulene	2.49
1458 [a]	1463	*allo*-aromadrendene	0.38
1465 [a]	1465	*cis*-muurola-4(14).5-diene	0.21
1478 [a]	1479	γ-muurolene	0.39
1484 [a]	1484	germacrene D	26.95
1495 [a]	1492	γ-amorphene	0.39
1500 [a]	1500	bicyclogermacrene	17.98
1504 [a]	1506	cuparene	1.68
1514 [a]	1513	β-curcumene	0.28
1514 [a]	1516	(*Z*)-γ-bisabolene	1.01
1522 [a]	1525	δ-cadinene	1.38
1529 [a]	1533	(*E*)-γ-bisabolene	1.06
1533 [a]	1539	*trans*-cadina-1.4-diene	0.09
1537	1544	(*E*)-α-bisabolene	0.21
1577 [a]	1581	spathulenol	0.96
1582	1587 [a]	caryophyllene oxide	0.31
1638	1643 [a]	*epi*-α-cadinol	0.33
1644	1649 [a]	α-muurolol	0.21
1652	1655 [a]	α-cadinol	0.31
	monoterpene hydrocarbons		9.30
	oxygenated monoterpenes		0.00
	sesquiterpene hydrocarbons		87.95
	oxygenated sesquiterpenes		2.12
	other		0.49
	TOTAL		99.86

RI_C, retention index, RI_L: retention index from the literature: (a) = [52] and (b) = [67]. Relative percentage areas calculated based on the peak areas.

Regarding the chemical composition, we can observe in Table 1, 32 volatile constituents were identified, accounting for 99.86% of the total, and sesquiterpene hydrocarbons dominated (87.95%), mainly germacrene D (26.95%), bicyclogermacrene (17.08%),

(*E*)-caryophyllene (17.06%), and δ-elemene (7.59%). In addition, the monoterpene hydrocarbon γ-terpinene (8.99%) had a high content. Turiel et al. [66] reported that (*E*)-caryophyllene was the major component of the EOs of *C. campestris* (23.90%) and *C. eriocladus* (24.10%), bicyclogermacrene was the main volatile compound of the EO of *C. chaetocalyx* (13.90%), and spatulenol was the component with the highest content in *C. glandulosus* EO (19.70%). The authors also found germacrene D at high levels in the EOs of *C. campestris* (13.70%), *C. eriocladus* (9.70%), and *C. chaetocalyx* (17.90%); (*E*)-caryophyllene in the EOs of *C. eriocladus* (7.10%) and *C. glandulosus* (8.90%); bicyclogermacrene in the EO of *C. glandulosus* (9.60%); and δ-elemene in the EOs of *C. chaetocalyx* (13.50%) and *C. glandulosus* (8.00%). The authors also noted that γ-terpinene was identified only in *C. campestris* EO, with a low content (0.70%). These results indicate that the present sample of *C. campinarensis* EO has a chemical composition similar to those of other species of this genus present in the Amazon region.

Germacrene D, the major constituent of the sample, shows larvicidal activity against the mosquito *Aedes aegypti* [68]. EOs containing this compound as a major component also have anti-inflammatory and anti-AChE properties [69]. (*E*)-Caryophyllene also has potential anti-inflammatory activity and can be used to treat central nervous system diseases, cancer, and dental caries infections caused by etiological agents [70].

Franco et al. [33] reported that germacrene D and (*E*)-caryophyllene have antioxidant activity, and bicyclogermacrene has been associated with larvicidal and antiviral activity. Figueiredo et al. [71] reported that EOs with high levels of γ-terpinene have moderate activity against food pathogens. According to Dang et al. [72], δ-elemene has anticancer activity against HeLa cells.

Da Silva Júnior et al. [73] reported that germacrene D, bicyclogermacrene and δ-elemene are directly related to plant defense mechanisms and have higher concentrations in the rainy season in the Amazon region. According to the authors, this concentration trend may be directly related to a plant strategy for attracting pollinating agents, especially bees and flies, which are common in the rainy season.

3.2. Antioxidant Capacity and Preliminary Toxicity of the Essential Oil

The Table 2, below shows the TEAC of the EO of *C. campinarensis*, measured through the inhibition of $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ radicals and its preliminary toxicity against *A. salina*.

Table 2. Trolox equivalent antioxidant capacity of *C. campinarensis* EO for inhibition of $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ radicals and preliminary toxicity against *A. salina*.

TEAC		Preliminary Toxicity	
ABTS (mM·L^{-1})	**DPPH (mM·L^{-1})**	**LC_{50} (μg·mL^{-1})**	**R^2**
0.55 ± 0.04 ^{a}	1.88 ± 0.08 ^{b}	20.84 ± 4.84	0.85

Values are expressed as the mean and standard deviation (n = 3) of Trolox equivalent antioxidant capacity. Student's t-test was used to compare OE of *C. campinarensis* to the Trolox standard (1 mM·L^{-1}). TEAC = Trolox equivalent antioxidant capacity. Different letters indicate that the samples are significantly different.

The TEAC of the EO to inhibit the $ABTS^{\bullet+}$ radical was 0.55 ± 0.04 mM·L^{-1} (p = 0.557). In the DPPH assay, the TEAC was 1.88 ± 0.08 mM·L^{-1} (p = 0.001). These results indicate that the $ABTS^{\bullet+}$ radical capture potential of the EO of *C. campinarensis* was lower than that presented by the Trolox standard (1 mM·L^{-1}). On the other hand, for the inhibition of $DPPH^{\bullet}$ radicals, the TEAC of the EO was almost double that of the Trolox standard (1 mM·L^{-1}). Regarding the preliminary toxicity against *A. salina*, the EO had an LC_{50} of 20.84 ± 4.84 μg·mL^{-1}. According to Ramos et al. [74], EOs with LC_{50} values lower than 80 μg·mL^{-1} are classified as toxic.

There are no reports in the literature regarding the antioxidant capacity and preliminary toxicity of *C. campinarensis* EO. However, other *Croton* species do have literature data on these properties. Morais et al. [75] reported that the evaluation of antioxidant activity by the DPPH method showed that *C. campinarensis* EOs have moderate antioxidant activity.

According to the authors, the Croton EOs did not contain phenolic compounds, which is the main cause of their lower antioxidant activity than the phenolic compound thymol and the commercial antioxidant BHT. In addition, the authors identified high levels of oxygenated sesquiterpenes in the samples, especially caryophyllene oxide and spathulenol. Pino et al. [76] found that the EO of *Croton wagneri* from Ecuador had a moderate elimination effect in the DPPH and ferric reducing antioxidant power (FRAP) assays. According to the authors, *cis*-chrysanthenol (27.5%) and myrcene (19.2%) were the major components of the sample.

Do Vale et al. [77] analyzed the antioxidant capacity of the EO of *Croton piauhiensis*, characterized by compounds such as (*E*)-caryophyllene (21.58%), γ-terpinene (10.08%), and germacrene D (9.56%). The authors indicated that this EO showed high antioxidant capacity in the DPPH test, with higher results than the positive control (quercetin).

Regarding preliminary toxicity, Ribeiro et al. [78] evaluated the preliminary toxicity of the EO of *Croton rudolphianus* leaves by bioassays with *A. salina*. According to the authors, this EO exhibited high toxicity to microcrustaceans (LC_{50} = 68.33 μg·mL^{-1}). In addition, the authors identified chemical constituents consistent with those found in the present sample, such as (*E*)-caryophyllene (17.33%), bicyclogermacrene (7.1%), and germacrene D (5.38%).

Andrade et al. [79] reported that the EO of *Croton zehntneri* leaves showed high toxicity against *A. salina*, with an LC_{50} of 4.54 μg·mL^{-1}. However, the authors found that phenylpropanoid estragol was the major compound in the sample (84.70%). Lawal et al. [80] reported that the EO of *Croton gratissimus* showed toxicity against *A. salina*, with an LC_{50} of 8.52 mg·mL^{-1}, corresponding to a classification of toxic. Regarding the chemical composition of the EO, the authors indicated that α-phellandrene (12.30%), β-phellandrene (10.70%), α-pinene (6.05%), and germacrene D (5.90%) were the major components.

Regarding the possible antioxidant capacity of the major components of the EO of *C. campinarensis*, EOs containing germacrene D, bicyclogermacrene, (*E*)-caryophyllene, γ-terpinene, and δ-elemene at high levels have shown relevant activity, scavenging ABTS$^{\bullet+}$ and DPPH$^{\bullet}$ radicals [81–85]. In addition, γ-terpinene can increase the protection of lipids and oxidizable substrates, in addition to prolonging the protective activity of the synthetic antioxidant α-tocopherol, making it a promising natural antioxidant for use in foods [86,87].

Regarding the toxicity of major compounds, Judzentienė et al. [88] reported that the EO of *Artemisia* vulgaris, containing high levels of germacrene D (10.60–30.50%), showed high toxicity against *A. salina*. The authors directly attributed the results to the presence of germacrene D in the sample. Machado et al. [89] reported that (*E*)-caryophyllene showed toxicity against *A. salina* only at high concentrations (3 mM). Schmitt et al. [90] showed that this sesquiterpene had no significant toxicity against rats.

Govindarajan et al. [91] stated that bicyclogermacrene showed high toxicity in mosquitoes of the species *Anopheles subpictus*, *Anopheles albopictus*, and *Culex tritaeniorhynchus*. De Oliveira et al. [92] found that the EO of *Lantana montevidensis* leaves, characterized by germacrene D (31.27%) and (*E*)-caryophyllene (28.15%), showed no fumigant toxicity in *Drosophila melanogaster* flies. EOs containing γ-terpinene and δ-elemene at high levels showed low toxicity against *A. salina* [93,94].

The biological properties of an EO may be associated with the major constituent of the sample and/or the synergistic and antagonistic effects exerted by all components present in the mixture [95]. Sesquiterpenes have higher toxicity than monoterpenes and phenylpropanoids [96]. Regarding free radical capture ability, sesquiterpenes generally have a lower antioxidant capacity than monoterpenes and phenylpropanoids [97]. These attributes may explain the antioxidant profile and preliminary toxicity exhibited by the EO of *C. campinarensis.*

3.3. Analysis of the Interactions of Major Compounds with AChE

In silico methods have been successfully used to evaluate the interaction between molecules of natural origin and molecular targets of pharmacological interest [98–101].

In this study, molecular docking was used to evaluate how the major compounds of *C. campinarensis* interact with the binding pocket of AChE, a molecular target related to toxicity that is investigated in *A. salina* models [45]. The energy values obtained for the interactions of the compounds with the target enzyme are summarized in Table 3.

Table 3. Moldock scores obtained from the docking protocol using MVD 5.5.

Molecule	MolDock Score	Rerank Score
Germacrene D	−01.107	−55.75
Bicyclogermacrene	−95.71	−71.41
(*E*)-caryophyllene	−103.70	−80.34
γ-terpinen	−49.42	−43.07
δ-elemene	−89.36	−70.84

The active site interactions are shown in Figure 1. Germacrene D established π-alkyl interactions with Tyr374, Tyr370, Phe371, Trp83, and Tyr71 (Figure 1A). The ligand bicyclogermacrene formed π-alkyl interactions with Tyr71, Tyr370, Tyr374, Trp472, and Trp83 (Figure 1B). For (*E*)-caryophyllene, the active site formed hydrophobic π-alkyl interactions with Trp472, Leu479, Trp83, Tyr71 Tyr374, and Tyr370 (Figure 1C). γ-Terpinene (8.99%) formed π-alkyl interactions with Tyr71, Tyr374, Trp83, Tyr370, Leu479, and Trp472 (Figure 1D). The binding of δ-elemene to the AChE binding pocket formed π-alkyl hydrophobic interactions with residues Tyr370, Tyr374, Tyr71, and Trp83 (Figure 1D).

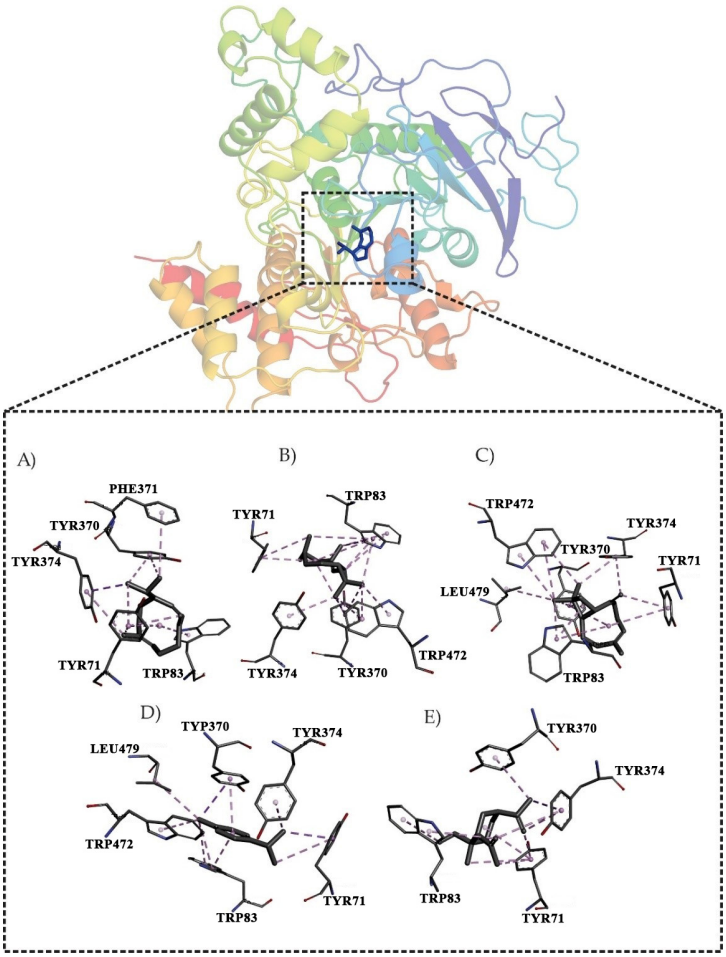

Figure 1. Molecular interactions in the binding pocket of AChE. Germacrene (**A**); bicyclogermacrene (**B**); (*E*)-caryophyllene (**C**); γ-terpinene (**D**); δ-elemene (**E**).

4. Conclusions

The yield of the *C. campinarensis* EO analyzed in this study was 0.24%. Terpenes characterized the aromatic profile of the EO, with a predominance of sesquiterpene hydrocarbons (87.95%), mainly germacrene D (26.95%), bicyclogermacrene (17.08%), (*E*)-caryophyllene (17.06%), and δ-elemene (7.59%). Regarding the antioxidant capacity of the EO, the evaluation of TEAC by the ABTS method showed that the EO has moderate antioxidant activity. However, the TEAC evaluation showed important inhibition of DPPH$^{\bullet}$ radicals. The preliminary cytotoxicity test against *A. salina* indicated that the EO of *C. campinarensis* can be classified as toxic, with an LC_{50} of 20.84 ± 4.84 μg·mL^{-1}. The energy calculations in Table 1 showed that complex formation was favorable. Hydrophobic interactions dominated the interactions between the major compounds of *C. campinarensis* EO and AChE. These results may indicate that the chemical components with higher contents in the sample may be related to the high toxicity demonstrated by the EO against the microcrustacean *A. salina*. This study presents the first report on the chemical composition, antioxidant capacity, and preliminary toxicity of the EO of *C. campinarensis*, contributing to the knowledge of the phytochemistry of species of the genus *Croton* from the Amazon region.

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