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Review

Essential Oils Of Caatinga Plants With Deletary Action For *Aedes Aegypti*: A Review

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ABSTRACT

In Brazil, *Aedes aegypti* mosquito is the most frequent vector of some arboviruses, such as dengue, yellow fever, Zika and chikungunya. The use of synthetic insecticides to combat this vector has been compromised due to the development of resistant populations and the collateral damage caused to nature. Essential oils (EO) have been studied as an alternative to synthetic insecticide. Thus, the objective of this work was to do a review of EOs from Caatinga biome plants, wich are effective against *Ae. aegypti* at different stage of development (eggs, larvae, pulp and adult); to identify promising plant species with insecticidal activity as well as the most frequent terpenic compounds in oils with the best activity profile. The keywords *Aedes aegypti*, essential oil, Caatinga and Northeast Brazil were searched on Scielo, Pubmed, 'Portal dos Periódicos Capes' and ScienceDirect platforms. Hence, a great insecticidal potential of these essential oils against *Ae. aegypti* larvae and adults was identified as well as great potential for repellents and oviposition supression. Of all the plants, those of genera *Cordia, Croton, Piper, Lippia* and several genera of the Lamiaceae family can be highlighted as the most promising against *Ae. aegypti*. Analyzing the oils that showed larvicidal activity at concetrations <100 ppm, β-Caryophyllene, Caryophyllene oxide, Spathulenol, 1,8-cineole and Thymol are common compounds in the majority and in all acetylcholinesterase inhibitory has been demonstrated. This study can assist the search for plant species with potential insecticide, including pointing out specific compounds that are promising for the development of applied research in the area.

1. Introduction

Several diseases are caused by etiologic agents that are transmitted through insect vectors, such as those belonging to the order Diptera. The World Health Organization (WHO) classifies some of these conditions as neglected tropical diseases, since they affect social economically vulnerable populations with little investment in their control and treatment development. Diseases such as dengue, yellow fever, Zika, chikungunya and other arboviruses are included in this category, whose main vector is the mosquito *Aedes aegypti* (WHO, 2017).

The *Ae. aegypti* mosquito belongs to the Culicidae family and is adapted to the urban environment with capacity to carry a large number of pathogens, which makes it an insect of health importance (Natal, 2002; Neves et al., 2004). Its life cycle begins in the egg, from which the larvae emerge. After four instars (stages), the larvae become pupae and then adult mosquitoes. Eggs can remain viable for a year or more even without the presence of water, representing a major threat for the mosquito control (Nelson, 1986; Neves et al., 2004). Its adult form is active mainly in the twilight hours, when the female mosquitoes blood feeds through the bite, which can also transmit arboviruses (Nelson, 1986; Natal, 2002).

Due to the lack of specific treatment for arboviruses, the most effective way to fight these diseases is by reducing the transmission of the pathogen through vectors combat. For this, chemical insecticides such as organochlorines and organophosphates have been the most used method to eliminate insects, having similar mechanisms of affecting the nervous system of these animals (Braga and Valle, 2007; Hickman et al., 2016). Despite their effectiveness, chemical pesticides can cause several unwanted effects. Organochlorines, such as the widely used DDT (dichloro-diphenyl-dichloro-ethane), present a long-term degradation and can accumulate in the lipophilic tissues of animals and reach humans through the food chain. Organophosphates are biodegradable and less persistent in the environment, but they are more unstable and need constant reapplication, also being toxic to humans (Carson, 2002; Braga and Valle; 2007; Karami-Mohajeri and Abdollahi, 2010; Mansouri et al., 2016).

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In addition to being potentially toxic to non-target organisms and contaminating soil and water, resistance to all classes of insecticides by several species of vectors are leading to the re-emergence of various diseases and bringing into question their traditional use (Brogdon and McAllister, 1998; Braga and Valle, 2007; Carson, 2002; WHO, 2017). In view of these issues, it is important to seek alternatives to combat these pests, such as the search for bioinsecticides derived from plants. Only a small percentage of insecticides on the market are based on those cited sources, including pyrethroids, pyrethrins and essential oils (Isman, 2000; Bakkali et al., 2008).

Essential oils (EO), which are complex mixtures of secondary metabolites (usually monoterpenes and sesquiterpenes) from aromatic plants, have received special attention due to their potential bioinsecticides and insect repellents (Isman, 2000; Bakkali et al., 2008). EOs show some advantages when compared to traditional chemical insecticides, such as their biodegradability, being species-specific and, in general, allowing low rate of resistance development in these organisms due to their several compounds (Isman, 2000; Bakkali et al., 2008).

Caatinga is an exclusively Brazilian biome with more than 1,500 plant species, many not found anywhere else in the world ([MMA] Ministério do Meio Ambiente, 2011). This biome has a strongly seasonal climate that alternates between short and irregular rainy seasons and long dry ones with variable duration, which can last months or years, depending on the region. Among all Brazilian formations, Caatinga has the highest solar radiation, plant evapotranspiration and average annual temperature, combined with low humidity and cloud cover (Leal et al., 2005; Giulietti et al., 2004). Due to these climatic and environmental conditions, Caatinga plants have developed unique chemical characteristics to deal with these environmental factors, being a great resource for bioprospecting relevant biological activities (Cartaxo et al., 2010).

Among the biological activities that Caatinga plants can provide, anti-inflammatory, antispasmodic, antitussive, antibiotic, insecticide and repellent effects have been described (Silva et al., 2012; Melo et al., 2015; Sá, 2018). However, most of the biodiversity of Caatinga remains unknown and it is of great importance that more studies be conducted, especially regarding the prospection of useful compounds to combat vectors of diseases such as *Ae. aegypti*. By doing so, public health will be improved by combating the transmission of arboviruses, in addition to promoting the preservation of this rich, but mostly unprotected biome (Albuquerque, 2006; [MMA] Ministério do Meio Ambiente, 2011). Bearing in mind the issues addressed, the objective of this work was to describe, through a bibliographic survey, essential oils from Caatinga plants that are effective in combating the insect *Ae. aegypti* in any of its development stages and identify in these oils the major terpenic compounds wich can be related to the insecticidal activity.

2. Materials and methods

2.1. Outline of keywords, platforms and search modes

To develop this work, a qualitative, bibliographic and exploratory research was carried out (Gil, 2002). A search for scientific papers was done on four research platforms, namely: ScienceDirect (https://www.sciencedirect.com/), 'Portal de Periódicos Capes' (https://www.periodicos.capes.gov.br/), Pubmed® (https://pubmed.ncbi.nlm.nih.gov/) and Scielo® (https://scielo.org/), in order to find studies on the use of essential oils from Caatinga plants to combat *Ae. aegypti* mosquito, regardless of publication period. The terms "*Aedes aegypti*" and "essential oil" were used as keywords, adding the terms "Caatinga" or "Northeast Brazil" in order to cover as many results as possible.

All results obtained in the search platforms were each one verified and filtered by title, summary and methodology, with the following criteria for the inclusion of the scientific work in this review:

I-Studies involving the specie *Aedes aegypti* (Culicidae);

II-The studied plants belonging to the Caatinga biome and

III-The tested sample was the plant essential oil, not other substances such as ethanolic extracts, fatty acids etc.

The online platform 'Flora do Brasil 2020', from Reflora, was used to check criterion II http://floradobrasil.jbrj.gov.br/reflora/listaBrasil/PrincipalUC/PrincipalUC.do (Reflora, 2020), where the scientific name of the species of the evaluated works was consulted to find out if these plants occurred in Caatinga biome.

This review excluded works in which the plant origin was not informed, the ones that were classified as cultivated in the Caatinga biome (i.e: ornamental plants, fruit trees of commercial interest etc.) by the 'Flora do Brasil 2020' platform or even those plants that despite occurring in the Caatinga were collected in other biomes or countries. In the case of works involving more than one plant species, only the results of those fitting the inclusion criteria were used. Therefore, this review was not limited to any specific period of time in order to gather as much information as possible.

2.3. In silico identification and characterization of insecticidal compounds

Essential oils that show the best larvicidal activity (LC_{50} <100 ppm) will have their chemical profiles compared to each other to identify similar compounds (among the major ones). This processing aims to perform the identification of compounds that are possibly responsible for the larvicidal activity. The selected compounds will be evaluated, *in silico* regarding the parameters of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET). The set of platforms used followed the methodology addressed by Barbosa et al (2020), which are: Swiss ADME, Swiss Target Prediction (SIB., Lausanne, Switzerland) PROTOX-II Server (Charité University, Berlin, Germany), Molinspiration (Molinspiration Chemin formatics, Nova Ulica, Slovakia), Osiris Property Explorer and Osiris Data Warrior (Actelion Pharmaceuticals Ltd., Allschwil, Switzerland). It was investigated, in the literature, if there are reports of acetylcholinesterase inhibitory activity shown by the selected compounds. The inhibitory activity of acetylcholinesterase is a common mechanism among insecticides and can serve as an indicator of this biological activity (França et al., 2021).

Reference structure information SMILES (Simplified Molecular-Input Line-Entry System) or InChi (International Chemical Identifier) were obtained from the PubChem database (CID codes: 5281515; 1742210; 92231; 13894537; 2758; 5317570; 6989).

2.4. Data analysis

The graphs and tables were made using Microsoft Word 2010 software (Microsoft ®) and GraphPad Prism 8.0. Software ACD labs Chemsketch (Toronto, On, Canada), version 14.0 was used to draw the structures.

3. Results and discussion

3.1. Status quo

The survey of data on the four platforms used (Pubmed®, Scielo®, 'Portal de Periódicos Capes' and Science Direct) identified 243 works. The largest number of papers was retrieved on the *Portal de Periódicos Capes* platform, with 154 papers, while the smallest amount was obtained on the Scielo platform, with two papers only.

After careful evaluation of the 243 works, only 13 papers met the inclusion criteria for this review. This value represents a 94.66% reduction in the total number of articles found. The amount of papers included, however, was slightly higher due to the references found on the work by Dias and Morais (2013). In this bibliographic review

Table 1
Families of Caatinga plants that had their essential oils evaluated in the fight against *Aedes aegypti* and the studies performed.

Families	N° of genera	N° of species	Studies performed			
			Larvicide	Adulticide	Repellent	Oviposition prevention
Annonaceae	2	2	X	-	X	-
Asteraceae	4	4	X	-	-	-
Begnoniaceae	1	2	X	-	-	-
Boraginaceae	1	1	X	-	-	-
Burseraceae	1	1	X	-	-	X
Euphorbiaceae	1	9	X	X	-	X
Lamiaceae	3	7	X	-	-	-
Myrtaceae	1	1	X	-	-	-
Piperaceae	1	4	X	-	-	-
Plantaginaceae	1	1	X	-	-	-
Poaceae	1	2	X	-	-	-
Rutaceae	1	1	X	-	-	-
Scrophulariaceae	1	1	X	-	-	-
Verbenaceae	2	5	X	-	X	-
Total	**23**	**41**				

The "X" indicates the presence of the study; "-" represents the absence of the study.

on essential oils from plants from around the world that were tested as larvicides against *Ae. aegypti*., 21 other references about essential oils from Caatinga plants that met the criteria were found, resulting in a total of 34 works reviewed in the present study.

Considering all the scientific papers reviewed, 54 essential oils from 41 plant species had their action studied against *Ae. aegypti*, these species belong to 23 genera and 14 different families (Table 1).

Regarding the studies on the mode of action of EO, four activities were highlighted on the chosen papers: larvicidal, adulticidal, repellent and oviposition prevention. The larvicidal activity of EO against *Ae. aegypti* can be considered the most extensively studied since all the articles evaluated the insecticidal activity of EOs against *Ae. aegypti* larvae (100%). Among the least explored are the adulticide and the oviposition prevention studies, which represented 5.55% of the total number of essential oils, followed by repellent studies (3.70%). Ovicidal and pupicidal activity, another ways of combating mosquito vectors, were absent in the works reviewed.

The Asteraceae family had the largest number of studied genera (*Ageratum, Baccharis, Pectis* and *Porophyllum*), followed by the Lamiaceae family (*Hyptis, Ocimum* and *Vitex*). The genus *Croton*, belonging to the Euphorbiaceae family, was the most widely studied, with the essential oils of nine species evaluated, followed by the genera *Piper* (Piperaceae), *Hyptis* (Lamiaceae) and *Lippia* (Verbenaceae), with the essential oils of four species studied in each one.

The 34 works used in this review were published between 2003 and 2020; the largest number of publications occurred in the years 2006, 2007 and 2010, each with four published works (Figure 1). The oldest publication found on the topic has the authorship of Carvalho et al. (2003), addressing the larvicidal activity of *Lippia sidoides* essential oil against *Ae. aegypti* mosquitoes. The most recent work is attributed to Cruz et al. (2020), regarding the larvicidal and adulticidal activity of a mixture of two essential oils from genus *Croton* against culicides, along with its toxicity on mice (*Mus musculus)*.

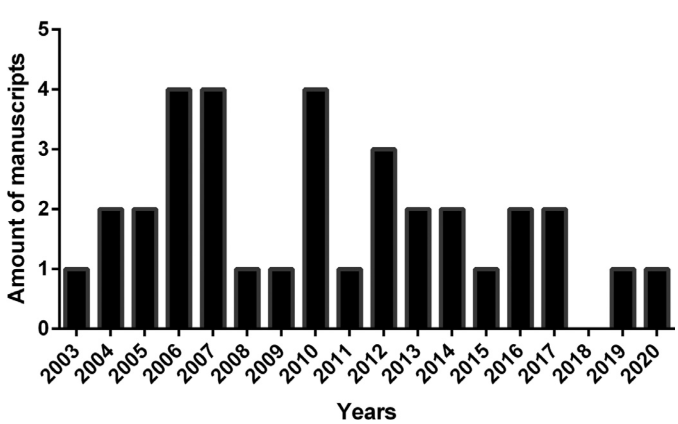

Figure 1. Number of manuscripts published per year on Caatinga plants essential oils against the Aedes aegypti mosquito.

3.2. Larvicidal activity studies

Considering the average lethal concentration (LC_{50}) (Table 2), 35 of the 54 essential oils studied (*Rollinia leptopetala, Cordia curassavica, Cordia leucomalloides, Auxemma glazioviana, Commiphora leptophloeos, Croton argyrophylloides, Croton nepetaefolius, Croton regelianus, Croton rhamnifolioides, Croton sonderianus, Croton zehntneri, Bauhinia acuruana, Hymenaea courbaril, Hyptis martiusii, Ocimum americanum, Ocimum gratissimum, Vitex gardneriana, Psidium guajava, Piper aduncum, Piper marginatum, Piper nigrum, Stemodia marítima, Cymbopogon citratus, Zanthoxylum articulatum, Capraria biflora, Lantana camara, Lippia gracilis Lippia pedunculosa, Pectis oligocephala* and *Lippia sidoides*) had an LC_{50} lower than 100 ppm and can be considered effective in attacking the mosquito larvae (Dias and Moraes, 2013). For instance, Albuquerque et al. (2007) observed that the essential oil of *P. oligocephala* at 100 ppm caused death to 100% of the larvae. Carvalho et al. (2003) also verified that the essential oil and the hydrolate (a by-product of the EO extraction) of *L. sidoides* leaves, diluted up to 10 times, caused 100% death of the larvae in less than 5 minutes of exposure, expanding the list of species to 37 essential oils.

Two studies compared the larvicidal potential of a given essential oil at different conditions. Santos et al. (2014) studied the larvicidal potential of *C. rhamnifolioides* essential oil comparing a freshly prepared to a stored one and found that the LC_{50} values were different between them (122.3 and 89 ppm, respectively). Silva et al. (2019) observed that the larvicidal activity of the *V. gardneriana* EO varied in the different collection months throught the year, with LC_{50} values ranging from 28 to 121.7 ppm. The composition of essential oils can change depending on storage conditions, such as the presence or absence of light (Misharina et al., 2003). In addition, climatic conditions (e.g. temperature, rainfall, solar radiation) directly affect the plant metabolism, causing changes in the composition and percentage of essential oil components (Globbo-Neto and Lopes, 2007).

The LC_{50} values of essential oils from the same parts of the plants studied by different authors showed some variation (Table 2). For example, the EO of *L. sidoides* leaves showed LC_{50} values of 63 and 19.5 ppm when studied by (Cavalcanti, 2004) and Costa et al. (2005), respectively. It is also perceivable that compounds from different

Table 2
Larvicidal activity of essential oils from Caatinga plants against *Aedes aegypti* larvae

Family/Specie/Popular name	Studied part	Origin	Main components of the EO	LC_{50} (ppm)	Reference
Annonaceae					
Rollinia leptopetala R.E. Fries	Leaves	Guaraciaba do Norte	Linalool and 1,8-cineole	104.70	Feitosa et al., 2009
	Stem	Guaraciaba do Norte, Ceará	Spathulenol	34.70	Feitosa et al., 2009
Xylopia laevigata Mart. (Pindaíba)	Leaves	Parque Nacional Serra de Itabaiana, Sergipe	Germacrene D and Bicyclogermacrene	>1000	Nascimento et al., 2017
Asteraceae					
Ageratum conyzoides L. (Mentrasto)	Leaves	Nordeste do Brasil	NI	148.00	Mendonça et al., 2005
Baccharis reticularia DC. (Alecrim-da-areia)	Leaves	Parque Nacional Restinga de Jurubatiba, Rio de Janeiro	D-limonene, (E)-caryophyllene and bicyclogermacrene	221.20	Botas et al., 2017
Pectis oligocephala Baker	Aerial parts	Sobral, Ceará	p-cymene and thymol	M	Albuquerque et al., 2007
Porophyllum ruderale (Jacq.) Cass	Leaves and flowers	Areia Branca, Sergipe	(E)-β-Ocimene	173.65	Fontes et al., 2012
Begnoniaceae					
Cordia curassavica (Jacq.) Roem. & Schult. (sábio negro)	Leaves	Crato, Ceará	α-pinene, β-pinene, (E)-caryophyllene and bicyclogermacrene	97.70	Santos et al., 2006
Cordia leucomalloides N.Taroda	Leaves	Crato, Ceará	δ-cadinene, (E)-caryophyllene, bicyclogermacrene and germacrene D	63.10	Santos et al., 2006
Boraginaceae					
Auxemma glazioviana Taub	Core	Cristais, Ceará	α-Bisabolol and α-cadinol	2,53*	Costa et al., 2004
Burseraceae					
Commiphora leptophloeos (Mart) J.B Gillet (Imburana-de-espinho)	Leaves	Parque Nacional Catimbau, Pernambuco	α-phellandrene,(E)-caryophyllene and β-phellandrene	99.40	Silva et al., 2015
Euphorbiaceae					
Croton argyrophylloides Muell. Arg. (Marmeleiro prateado)	Leaves	Viçosa do Ceará	α-pinene	102.00	Morais et al., 2006
Croton argyrophylloides Muell. Arg. (Marmeleiro prateado)	Leaves	Floresta Nacional Contendas do Sincorá, Bahia	NI	310.00	Cruz et al., 2020
	Aerial parts	Viçosa do Ceará, Ceará	β-trans-guaiene	94.60	Lima et al., 2013
Croton heliotropiifolius Kunth. (Velame)	Leaves	Aracaju, Sergipe	β-caryophyllene, bicyclogermacrene and germacrene D	544.00	Dória et al., 2010
	Leaves	Aracaju	β-caryophyllene	550.68	Silva, 2006
Croton nepetaefolius Baill (Marmeleiro sabiá)	Leaves	Viçosa do Ceará, Ceará	Methyleugenol	84.00	Morais et al., 2006
	Aerial parts	Viçosa do Ceará, Ceará	Methyleugenol	66.40	Lima et al., 2013
Croton pulegiodorus Baill. (Velaminho)	Leaves	Aracaju, Sergipe	β-caryophyllene, bicyclogermacrene, germacrene D, τ-cadinol and β-copaen-4-α-ol	158.81	Dória et al., 2010; Silva et al., 2006
Croton regelianus Müll. Arg. (velame-de-cheiro)	Leaves	Acarape, Ceará	Ascaridole	24.20*	Torres, 2008
Croton rhamnifolioides Pax & K. Hoffm	Leaves	Serra Talhada, Pernambuco	Sesquicineole, 1,8-Cineole and α-phellandrene	89.00*	Santos et al., 2014
Croton sonderianus Muell. Arg. (Marmeleiro preto)	Leaves	Viçosa do Ceará, Ceará	β-phellandrene and β-transguaiene	104.00	Morais et al., 2006
	Aerial parts	Viçosa do Ceará, Ceará	Spathulenol	54.50	Lima et al., 2013
Croton tetradenius Baill. (Catinga-de-bode)	Leaves	Floresta Nacional Contendas do Sincorá, Bahia	Camphor and γ-Terpineol	152.00	Carvalho et al., 2016
	Leaves	Floresta Nacional Contendas do Sincorá, Bahia	NI	150.00	Cruz et al., 2020
Croton zehntneri Pax & Hoffm (Canela de cunhã)	Leaves	Viçosa do Ceará, Ceará	(E)-Anethole	28.00	Morais et al., 2006
	Leaves	Tianguá, Ceará	(E)-Anethole	56.20	Santos et al., 2007
	Aerial parts	Viçosa do Ceará	(E)-Anethole	26.20	Lima et al., 2013
	Stem	Tianguá, Ceará	(E)-Anethole and *p*-anisaldehyde	51.30	Santos et al., 2007
	Roots	Tianguá, Ceará	(E)-Anethole	57.50	Santos et al., 2007
Croton argyrophylloides Muell. Arg.+ *Croton tetradenius* Baill.	Leaves	Floresta Nacional Contendas do Sincorá, Bahia	Camphor, isopinocampheol and (E)-caryophyllene	160.00	Cruz et al., 2020
Fabaceae					
Bauhinia acuruana Moric	Leaves	Tianguá, Ceará	Epi-α-cadinol and spathulenol	56.20	Gois, 2014
Hymenaea courbaril L.	Ripe fruit peel	Crato, Ceará	α-Copaene and espathulenol	14.80	Aguiar et al., 2010
	Immature fruit peel	Crato, Ceará	Germacrene D and β-caryophyllene	28.40	Aguiar et al., 2010
Lamiaceae					
Hyptis fruticosa Salzm. Ex Benth	Leaves	São Cristóvão, Sergipe	1,8-Cineole	502.00	Silva et al., 2008
Hyptis martiusii Benth	Leaves	Floresta Nacional do Araripe, Ceará	δ-3-Carene and 1,8-cineole	18.50	Costa et al., 2005
Hyptis pectinata (L.) Poit	Leaves	São Cristóvão, Sergipe	β-Caryophyllene and caryophyllene oxide	366.00	Silva et al., 2008
Hyptis suaveolens Poit (Cheirosa)	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	1,8-Cineole, trans-caryophyllene and β-Pinene	261.00	Cavalcanti, 2004
Ocimum americanum L. (Alfavaca-do-campo)	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	E-Methyl-cinnamate and Z-methyl-cinnamate	67.00	Cavalcanti, 2004

(*continued*)

Table 2 (*Continued*)

Family/Specie/Popular name	Studied part	Origin	Main components of the EO	LC_{50} (ppm)	Reference
Ocimum gratissimum L. (Alfavacão)	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	Eugenol and 1,8-Cineole	60.00	Cavalcanti, 2004
Vitex gardneriana Schauer. (Jaramataia)	Leaves	Fazenda experimental (UVA), Sobral, Ceará	6.9-guaiadiene, cis-calamenene and caryophyllene oxide	28.00*	Silva et al., 2019
Myrtaceae					
Psidium guajava L. (Goiabeira)	Leaves	Fortaleza, Ceará	1,8-Cineole and β-Caryophyllene	24.70	Lima et al., 2011
Piperaceae					
Piper aduncum L.	Fruits	Crato, Ceará	β-Pinene	30.20	Costa et al., 2010a
Piper marginatum Jacq	Leaves	Crato, Ceará	Isoelemecine and apiole	8.29	Costa et al., 2010a
Piper nigrum L.	Seeds	Crato, Ceará	(E)-Caryophyllene, caryophyllene oxide and sabinene	75.80	Costa et al., 2010a
Piper tuberculatum Jacq. (Pimenta-de-macaco)	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	(E)-caryophyllene, γ-muurolene, α-pinene and β-pinene	106.30	Lavor et al., 2012
Plantaginaceae					
Stemodia maritima L.	Leaves	Freixeiras, Ceará	β-Caryophyllene	55.40	Arriaga, 2007
	Stem	Freixeiras, Ceará	β-Caryophyllene and caryophyllene oxide	22.90	Arriaga, 2007
Poaceae					
Cymbopogon citratus Stapf (capim-cidreira)	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	Geranial and neral	69.00	Cavalcanti, 2004
Cymbopogon flexuosus (Nees ex Steud.) Wats (capim-limão)	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	Geranial and neral	121.60	Lavor et al., 2012
Rutaceae					
Zanthoxylum articulatum Engler (limãozinho)	Leaves	Jacobina, Bahia	Viridiflorol	77.62	Feitosa et al., 2007
Scrophulariaceae					
Capraria biflora L.	Leaves	Itapiúna, Ceará	α-Humulene	73.39	Souza, 2012
Verbenaceae					
Lantana câmara L.	Leaves	Crato, Ceará	Bicyclogermacrene and (E)-caryophyllene	42.30	Costa et al., 2010b
Lippia gracilis Schauer	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	Carvacrol	26.30	Santiago, 2006
	Leaves	Vila do Feijão, São Cristóvão, Sergipe	Carvacrol	98.00	Silva et al., 2008
Lippia pedunculosa Hayek.	Leaves	Povoado Cajueiro, Poço Redondo, Sergipe	Piperitenone oxide and limonene	58.00	Nascimento et al., 2017
Lippia rigida Schauer.	Leaves	Mucuge, Bahia	α-humulene and β-caryophyllene	138.90	Oliveira et al., 2016
Lippia sidoides Cham. (alecrim-pimenta)	Leaves	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	Thymol	63.00	Cavalcanti, 2004
Lippia sidoides Cham. (alecrim-pimenta)	Leaves	Horto Florestal Municipal, Crato, Ceará	Thymol	19.50	Costa et al., 2005
	Sprouts	Horto das Plantas Medicinais (UFC), Fortaleza, Ceará	Thymol and carvacrol	M	Carvalho et al., 2003

EO: Essential oil
LC_{50}: Lethal Concentration 50
ppm: Parts per million
NI: No information
M: Result expressed as dead larvae percentage (Mortality)
***:** Lowest LC_{50} value obtained in the study for essential oil

organs can also show different insecticidal potential, as seen in *R. leptopetala* EO, which presented LC_{50} of 104.7 and 34, 7 for its leaf and stem, respectively. That variation was also observed with different parts of *C. argyrophylloides* and *C. sonderianus* plants.

As for the main components of essential oils, those listed below, caryophyllene, caryophyllene oxide, 1,8-cineole, bicyclogermacrene, thymol and sphatulenol can be highlighted as the possible compounds responsible for the effective larvicidal action, since the most times they appeared as major compounds in different plant species an LC_{50} less than 100 ppm was observed. Regarding this value, most of the plants of genera *Cordia, Croton, Lippia* and *Piper*, as well as the three genera of Lamiaceae family, had representatives with LC_{50} values below 100 ppm, being effective as larvicides and, thus, having potential biotechnological application in combating *Ae. aegypti*.

It was observed that 68.51% of essential oils were effective in eliminating *Ae. aegypti* larvae. This shows the enormous potential that Caatinga flora has in combating the aforementioned vector, an insect of great importance for health. In addition, when obtained by economically viable means, the essential oils can be a much cheaper form of insecticide to combat this mosquito (Dias and Moraes, 2013). Hence, bioprospection of EO should be encouraged for better understand the role of their compounds role against *Ae. aegypti* larvae or other disease vectors. At very least, it is essential that this knowledge becomes a benefit for the population, especially the most socioeconomically vulnerable, thus drawing attention to the Caatinga study and preservation ([MMA] Ministério do Meio Ambiente, 2011; Dias and Morais, 2013; WHO, 2017).

3.3. Adulticidal activity studies

Two studies evaluated the adulticidal activity of essential oils from *Croton* genus (Table 3). Carvalho et al. (2016) studied the EO of *Croton tetradenius* leaves, as well as Cruz et al. (2020). The latter also studied the insecticidal potential of the EO from *C. argyrophilloides* leaves and the mixture of these two oils against the female adults of *Ae. aegypti* mosquito. Those three essential oils showed efficacy as insecticides against female mosquito with 70 to 95% mortality after 24 h of exposure to the compounds. Both studies also evaluated the

Table 3
Adulticidal activity of essential oils from Caatinga plants against the *Aedes aegypti* mosquito.

Famíly/Specie/Popular name	Main components of EO	Mortality (%) x exposure time (hours)							Reference	LC_{50}* (mg/mL)	Reference
		1	12	24	36	48	60	72			
Euphorbiaceae											
Croton argyrophylloides Muell. Arg. (Marmeleiro prateado)	NI	33.7	77.5	90.0	95.0	100.0	100.0	100.0	Cruz et al,2020	5.92	Cruz et al., 2020
Croton tetradenius Baill. (Catinga-de-bode)	NI	34.2	82.5	95.0	97.0	100.0	100.0	100.0	Cruz et al,2020	1.84/1.842	Cruz et al., 2020/ Carvalho et al., 2016
Croton argyrophylloides Muell. Arg.+ *Croton tetradenius* Baill	Camphor, isopinocampheol and (E)-caryophyllene	30.8	60.0	70.0	85.8	92.5	93.3	93.3	Cruz et al,2020	0.75	Cruz et al., 2020

mg/mL: Miligram per mililitre
LC_{50}*: Lethal concentration 50 after 24 hours
NI: No information

Table 4
Repellent activity of essential oils from Caatinga plants against the mosquito *Aedes aegypti*

Family/Specie/Popular name	Studied part	Origin	Main components of EO	RD_{50}/RD_{90} Concentration (%)	Reference
Annonaceae					
Xylopia laevigata Mart. (Pindaíba)	Leaves	Parque Nacional Serra de Itabaiana, Sergipe	Germacrene D and bicyclogermacrene	1.82 / 7.87	Nascimento et al., 2017
Verbenaceae					
Lippia pedunculosa Hayek.	Leaves	Povoado Cajueiro, Poço Redondo, Sergipe	Piperitenone oxide and limonene	0.49 / 1.08	Nascimento et al., 2017

EO: Essential oil
RD_{50}: Repellent dose 50
RD_{90}: Repellent dose 90

toxicity of these essential oils on mice (*Mus musculus*) and found low toxicity to this mammal (2000 mg/kg), an evidence of its safety as a potential insecticide (Cruz et al., 2020; Carvalho et al., 2016). Also regarding Cruz et al. (2020) work, the combination of the essential oils of *C. argyrophylloides* and *C. tetradenius* promoted a synergistic action and increased the toxicity of the oils to the insect while decreasing the *C. tetradenius* toxicity to mice. These results highlight the possibilities yet to be achieved with further studies of these preparations.

Other authors studied the adulticidal action of essential oils from other plants against *Ae aegypti* and it is possible to see, by comparison with the previously shown results, that they can be considered satisfactory. Dua, Pandey and Dash (2010) studied the adulticidal action of *Lantana camara* essential oil on *Ae. aegypti* and observed 93,3% of mortality 24 h after exposure, also demonstrating effect against malaria vector mosquitoes of the genus *Anopheles* (100% mortality). Chaiyasit et al. (2006) studied five essential oils from four different families (*Apium graveolens, Carum carvi, Curcuma zedoaria, Piper longum* and *Illicium verum*) and observed that the EO caused between 85 and 88% of mortality after 24 h after exposure to the compounds.

These results indicate that Caatinga plants can be used to combat female adults of *Ae. aegypti* mosquito, wich are directly responsible for transmitting arboviruses. However, the studies are still insufficient to draw definitive conclusions.

3.4. Repellency studies

Only one study was found about repellency of essential oils against *Ae. aegypti*. Nascimento et al. (2017) studied the potential of the EO of *Xylopia laevigata* and *Lippia pedunculosa* leaves to repel that mosquito (Table 4). The two essential oils tested showed some degree of protection against the bites of *Ae. aegypti* females. The essential oil of *X. laevigata* showed RD_{50} (Repellent Dose $_{50}$, i.e. the amount of EO necessary to avoid half of insect bites) of 1.82%. This value quadrupled when analyzing the concentration necessary to avoid 90% (RD_{90}) of insect bites (7,87%). However, this EO showed low yield and would require large amounts of vegetable biomass to obtain it in a satisfactory quantity for protection against the mosquito, making its use practically unfeasible (Nascimento et al., 2017). The essential oil of *L. pedunculosa*, on the other hand, showed a high repellent action, avoiding up to 90% of the bites at a concentration close to 1% (Table 4). This essential oil proved to be quite effective in preventing *Ae. aegypti* bites in small amounts, which makes this preparation a candidate for an alternative repellent to prevent the transmission of diseases by this vector (Nascimento et al., 2017). For that, further studies to assess the toxicity of this EO compounds to humans are needed, since its use involves direct skin contact.

Repellents act by creating a protective strip on the surface where they are applied, preventing insects and/or other arthropods from coming into contact with the user, thus avoiding possible bites (Nerio et al., 2010). These are of great importance for health, as they can protect against vectors bites, such as those of *Ae. aegypti*, upon entering areas with these mosquitos infestation. DEET (N, N-dimethyl-meta-toluamide) is the main insect repellent known today, but it has some disadvantages such as some degree of toxicity to skin and to the nervous and immune systems (usually when the product is not used correctly) (Choochote et al., 2007). Due to the importance of having products with less adverse effects, it is critical to identify alternatives such as essential oils with repellent action in order to avoid direct contact of these vectors with humans, thus generating a more immediate response in preventing disease transmission even during outbreaks and infestations.

3.5. Oviposition suppression studies

Two studies were found that evaluated the ability of essential oils to suppress the oviposition of pregnant *Ae. aegypti* females: one from *C. leptophloeos* leaves (Silva et al., 2015) and the other from *C.*

Table 5
Effects of essential oils from Caatinga plants on the suppression of oviposition of pregnant females of the *Aedes aegypti* mosquito

Family/Specie/ Popular name	Studied part	Main components of EO	Oviposition site	Approximate proportional value of eggs laid (%) in different concentrations (ppm)				Reference
				10 ppm	25 ppm	50 ppm	100 ppm	
Burseraceae *Commiphora leptophloeos* (Mart) J.B Gillet (Imburana-de-espinho)	Leaves	α-phellandrene, (E)-caryophyllene and β-phellandrene	**Control**	58%	62%	65%	60%	Silva et al., 2015
			EO	42%	38%	35%	40%	
Euphorbiaceae *Croton rhamnifolioides* Pax & K. Hoffm	Leaves	Sesquicineole, 1,8-Cineole and α-phellandrene	**Control**	-	-	$68\%^{A}$/ $82\%^{B}$	$75\%^{A}$ / $75\%^{B}$	Santos et al., 2014
			EO	-	-	$32\%^{A}$/ $18\%^{B}$	$25\%^{A}$/ $25\%^{B}$	

EO: Essential oil
ppm: Parts per million
X^{A}: Fresh essential oil result
X^{B}: Stored essential oil result
-: Not studied

Table 6
In silico ADMETa analysis of major constituents of oils with larvicidal activity (<100 ppm) and AChE inhibition potential

Property	Selected compounds				
	β-Caryophyllene	Caryophyllene oxide	Spathulenol	1,8-cineole	Thymol
PHYSICOCHEMICAL PROPERTIES					
HBA	0	1	1	1	1
HBD	0	0	1	0	1
cLogP	5.82	3.68	3.26	2.67	2.80
M/W (g/mol)	204.35	220.35	220.35	154.25	150.22
n-ROTB	0	0	0	0	1
ABSORPTION					
BBB	No	Yes	Yes	Yes	Yes
GIA	Low	High	High	High	High
P-GPs	No	No	No	No	No
Log Kp (cm/s)	-4.44	-5.12	-5.44	-5.30	-4.87
METABOLISM					
CYP450 2C9 inhibitor	Yes	Yes	No	No	No
CYP450 2D6 inhibitor	No	No	No	No	No
CYP450 2C19 inhibitor	Yes	Yes	Yes	No	No
CYP450 3A4 inhibitor	No	No	No	No	No
CYP450 1A2 inhibitor	No	No	No	No	Yes
Possible human target	PPARA/CNR2	SQLE/LSS	UGT2B7/ HSD11B1	CYP19A1/ SHH	TRPA1/ PTGS1
TOXICITY					
Toxicity Class	5	5	5	5	4
Mutagenic	Low risk	Low risk	Low risk	Low risk	Low risk
Tumorigenic	Low risk	Medium risk	High risk	Low risk	Low risk
Ittitant	Low risk	Low risk	High risk	Low risk	Low risk
Hepatotoxic	Low risk	Low risk	Low risk	Low risk	Low risk
Reproductive effective	Low risk	Medium risk	Low risk	Medium risk	Medium risk
LD_{50} (mg/kg)	5300.00	5000.00	3900.00	2480.00	640.00
AChE inhibitor	*32% (0.06 mM) (Bonesi et al., 2010)	*35% (0.25 mg/mL) (Savelev et al., 2003)	* 49.1% (100 μM) (Tundis et al., 2016)	** 0.06 mg/mL (Savelev et al., 2003)	**0.74 mg/mL (Jukic et al., 2007)

ADMET: absorption, distribution, metabolism, excretion and toxicity; **HBA**: Number of hydrogen force acceptors; **HBD**: Number of hydrogen donors; **cLogP**: Is the logarithm of its partition coefficient between n-octanol and water log (coctanol/cwater), is a well-established measure of the compound's hydrophilicity; **n-ROTB**: Number of rotary connections **MW**: Molecular Weight; **BBB**: blood-brain barrier; **GIA**: gastrointestinal absorption; **P-GPs**: permeability glycoprotein; **Log Kp (cm/s)**: Skin permeation; **CYP450**: Cytochrome P450 Enzyme; **LD_{50}**: lethal dose at 50%; **PPARA** – Peroxisome Proliferator Activated Receptor Alpha; **CNR2** - Cannabinoid Receptor 2; **SQLE** -Squalene Epoxidase; **LSS** - Lanosterol Synthase; **UGT2B7** - UDP Glucuronosyltransferase Family 2 Member B7; **HSD11B1**- Hydroxysteroid 11-Beta Dehydrogenase 1; **CYP19A1** - Cytochrome P450 Family 19 Subfamily A Member; **SHH** - Sonic Hedgehog Signaling Molecule; **TRPA1** - Transient Receptor Potential Cation Channel Subfamily A Member 1; **PTGS1**- Prostaglandin-Endoperoxide Synthase 1; NF: Not found; *Concentration of compound (treatment) required for 50% enzyme inhibitionas calculated from the dose–response curve; **The percent AChE inhibition values (1.0 mM) were calculated as compared to control (without terpenoids) enzyme activity (assumed to be 0% inhibition).

rhamnifolioides (Santos et al., 2014). The latter also evaluated the difference in the effectiveness of the oil in its fresh and stored state (Table 5).

In an oviposition suppression study, it is evaluated whether the tested product is able to completely reduce or prevent the laying of eggs by female insects on the local where this compound is present, compared to a control model. The two essential oils studied showed some degree of suppression of oviposition. Additionally, Santos et al. (2014) noticed that, as occurred in the larvicidal activity, the essential oil of *C. rhamnifolioides* showed better results when used in stored form rather than fresh. Comparing the proportional numbers of eggs placed in the concentration of 50 ppm in both works, only 18 and 35% of eggs were placed in the oviposition sites by *Ae. aegypti* females when these essential oils were present (Table 6). Despite partially avoiding oviposition, the results observed by those authors were not as promising as those of other essential oils. For instance, those of *Cinnamomum zeylanicum* and *Zingiber officinale*, which are India plants studied by Prajapati et al. (2005). These oils inhibited by 95% eggs placement when their EOs concentrations were 81.9 and 106.7 ppm, respectively, on the insect's oviposition sites. On a similar

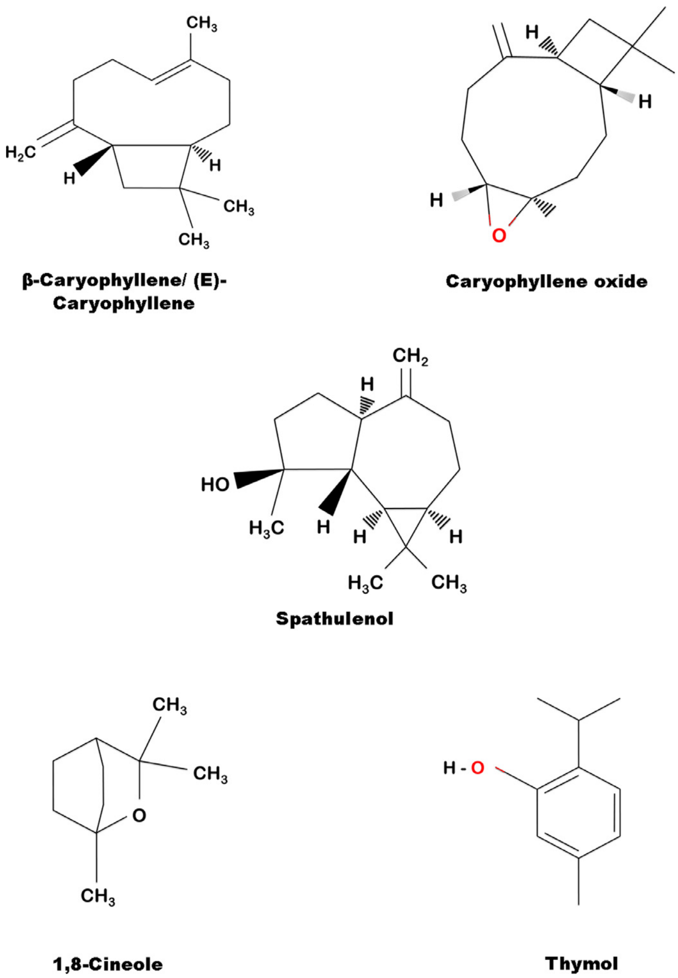

Figure 2. Chemical structure major constituents of oils with AChE inhibition potential and larvicidal activity (<100 ppm).

way, the essential oil of *Schefflera leucanta*, also from India, prevented by 91.6% the eggs laying of *Aedes aegypti* pregnant females at a concentration of 100 ppm (Tawatsin et al., 2006).

Considering these facts, it is possible to infer that only the stored EO of *C. rhamnifoliodes* leaves at 50 ppm studied by Santos *et al.* (2014) showed results that could indicate its practical use in the future. Nevertheless, further studies on the safety of this essential oil to other non-target organisms are necessary before any practical use of this product.

3.6. Main compounds of essential oils with larvicidal activity

The comparison of the major compounds present in 35 essential oils that showed larvicidal capacity at a concentration less than 100 ppm or a high mortality rate allowed the identification of 5 compounds that occur frequently (Figure 2): β-caryophylene/(e)-caryophylene that appeared in the oil composition oils of *C. curassavica, C. leucomalloides, C. leptophleos, H. courbaril, P. guajava, P. nigrum, S. maritima* and *L. camara*; Caryophylene oxide that appeared in the composition of oils of species *V. gardneriana, P. nigrum* and *S. maritima*; Spathulenol that appeared in the composition of oils of species *R. leptopetala, C. sonderianus, B. acuruana* and *H. courbaril*; 1,8-cineole that appeared in the composition of oils of species *C. rhamnifolioides, H. martiusii, O. gratissimum* and *P. guajava* and Thymol that appeared in the composition of oils of species *P. oligocephala* and *L. sidoides* (Table 2).

The safe development of drugs and products requires a deep knowledge of the characteristics of the active ingredients. In this sense, to better understand the specific characteristics of terpenic compounds, an *in silico* investigation of the ADMET characteristics was performed (Table 6). According to Barbosa et al. (2020), the physicochemical properties suitable for a molecule to be absorbed by the gastrointestinal tract include a molecular mass of 150 to 500 g/mol, a number of hydrogen bond acceptors less than 10, a cLogP of 0 at 5 and a number of hydrogen donors below 5. Considering these ranges of values all compounds showed acceptable values for gastrointestinal absorption. In fact, the prediction of the absorption capacity showed that at least four of the compounds may have a high absorption capacity through the gastrointestinal tract as well as the ability to cross barriers as highly selective as the blood-brain barrier.

As for metabolism, most compounds appear to interact with CYP450 2C9 and 2c19, which are common enzymes for the metabolism of xenobiotics and other drugs (Rettie and Jones, 2004; Andrade et al., 2018). As for possible genetic targets, it is interesting to note that three of the compounds converged to the genes PPARA - Peroxisome Proliferator Activated Receptor Alpha and CNR2 - Cannabinoid Receptor 2. The activation of PPRA induces an increase in the number of peroxisomes, influencing the metabolism of cholesterol and lipids in general (Golembesky et al., 2008), the lipophilic character and structural similarity may have an influence on this aspect. Terpenic compounds have already been directly associated with the activation of CNR2, such as the β-caryophylene mentioned in this work, and this event in humans points to possible therapeutic uses since activation in CNR2 is involved in strategies for the treatment of inflammation, pain, atherosclerosis and osteoporosis (Gertsch et al., 2008). Concerning toxicity, in general, the compounds have a low possibility of toxicity in several aspects and an LD50 with values mostly greater than those recommended by OECD 423 for acute oral toxicity that has a limit of 2000 mg/kg.

Among neuroactive compounds, those that have the ability to inhibit the enzyme acetylcholinesterase as a mechanism of action are the most common among insecticides (Casida and Durkin, 2013). Different levels of acetylcholinesterase inhibition capacity by the selected terpenic compounds have been reported, indicating a possible mechanism of action, and that the presence of these in oils can be predictive for insecticidal activity by this route.

4. Conclusion

This bibliographical survey highlighted the effectiveness of essential oils from Caatinga plants in combating *Ae. Aegypti* mosquito, especially in its larval stage. Caryophyllene, 1,8-cineole, thymol, caryophyllene oxide and sphatulenol are the compounds with LC_{50} less than 100 ppm most frequently found in these essential oils and probably the responsible for their larvicidal effect. Essential oils from the plant genera *Cordia, Croton, Lippia* and *Piper* and from the Lamiaceae family proved to be the most promising in attacking this vector mosquito. Therefore, these essential oils can be an alternative resource in combating the larvae of *Ae. Aegypti*. Anyhow, further studies will better elucidate the knowledge on this matter for the correct use of these volatile compounds.

Authorship Contributions

Daniel M. Marques and Thiago S. Almeida, performed the bibliographic investigation and analysed results as also carried out the statistical analysis. Thiago S. Almeida, Joanna F. Rocha and Erika F. Mota wrote the report and designed the research.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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