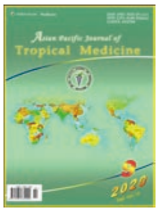

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Larvicidal efficacy of plant extracts and isolated compounds from Annonaceae and Piperaceae against *Aedes aegypti* and *Aedes albopictus*

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ABSTRACT

The *Aedes* (*Ae.*) *aegypti* and *Ae. albopictus* mosquitoes are vectors of epidemiologically relevant arboviruses in the public health context, such as the dengue, Zika and chikungunya viruses. Among the alternatives to synthetic insecticides for the control of these vectors, the use of natural plant products deserves attention. This review summarizes findings on the larvicidal potential of plant extracts on *Ae. aegypti* and *Ae. albopictus*, as well as the potential of isolated compounds from plants of the Annonaceae and Piperaceae families against these vectors. Descriptors related to larvicidal activity of plant extracts and isolated compounds in *Aedes* spp. in the Web of Science database were used, for plant extracts considering publications between 2000 and 2019. A total of 859 articles were analyzed for plant extracts and estimates of lethal concentration values (LC_{50} and LC_{90}). In the end, 95 articles that presented the larvicidal potential of 150 plant species from 52 families were analyzed. The two families most studied for this activity were Fabaceae and Asterace *Aedes*. The plant families with the best LC_{50} values against mosquitoes were Piperaceae and Annonaceae. Larvicidal activity of 50 acetogenins has already been identified on *Ae. aegypti*, and 29 of them presented LC_{50} below 10 μg/mL, as well as the larvicidal activity of 8 compounds isolated from Piperaceae. Therefore, plants of these two families are promising for the development of commercial botanical larvicides in the form of extracts and isolated substances, as well as the production via organic synthesis of the most active compounds.

KEYWORDS: Larvicidal activity; Plant extracts; Acetogenins; *Aedes*

1. Introduction

Dengue, chikungunya and Zika viruses are emerging arboviruses in tropical countries such as Brazil, being spread mainly by *Aedes* (*Ae.*) *aegypti*[1] and *Ae. albopictus*[2]. Lately, the flow of people between continents has increased the transmission of these arboviruses, which has prompted numerous efforts to implement control strategies, given the lack of effective vaccines against their etiological agents[3]. Thus, several strategies have been developed to control *Ae. aegypti* mosquitoes including mechanical controls such as elimination of breeding sites, reservoir drainage, and installation of screens on doors and windows; biological controls such as the use of fish and invertebrates that feed on immature stages of mosquitoes, the use of fungi and bacteria that produce lethal toxins to *Aedes*; and chemical controls such as the use of neurotoxic substances, and juvenile hormone analogs or chitin synthesis inhibitors to eliminate these vectors[4].

Plants have several bioactive compounds that are necessary

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for their survival against attacks by herbivorous pathogens and animals[5]. Several substances are accumulated and used in defense; some of them containing volatile compounds (acids, aldehydes and terpenes), which are produced and released to attract pollinating agents as well as to defend against herbivores. Among the classes of substances of plant origin with proven larvicidal activity are amides, quinones, flavonoids, rotenoids, chromanones, prenylated stilbenes, phenylpropanoids, coumarins, alkylphenols, lignans, lactones, monoterpenes, sesquiterpenes, diterpenes, triterpenes, limonines, saponins, quassinoids and alkaloids[6].

Plant extracts are mixtures of secondary metabolites with wide applications such as bioinsecticides. They can be obtained from roots, stems, leaves, flowers, fruits and seeds using solvents with different polarities[7,8].

Substances obtained from many plants are used in folk medicine, due to active principles that provide benefits against various diseases and conditions. In this respect, plants of the Annonaceae family are widely used in traditional medicine for a range of human diseases, such as cancer and parasitic diseases[9]. In particular, an acetogenin-rich fraction and annonacin isolated from the ethanolic extract of *Annona* (*A.*) *muricata* L. were found to be active against *Ae. aegypti* and *Ae. albopictus* larvae[8].

Given the wide dispersion of *Aedes* mosquitoes and the consequent increase in the risk of transmission of pathogens carried by them, there is a need for alternative vector control measures to minimize the environmental impacts of substances such as synthetic insecticides. Therefore, it is necessary to identify the families of plants with the greatest potential for the control of vector mosquitoes and the isolated compounds that can serve as a basis for the synthesis of industrial larvicides. This study examines the larvicidal potential of plant extracts and compounds isolated from plants of the families Annonaceae and Piperaceae against *Ae. aegypti* and *Ae. albopictus*.

2. Methods and criteria for literature selection

We selected the articles with a focus on larvicidal activity against *Ae. aegypti* and *Ae. albopictus* of plant extracts and acetogenins isolated from plants of the Annonaceae family, available in the Web of Science database, using the following control descriptors: "plant extract", "larvicidal activity", "mosquito", "*Aedes*", "acetogenins", "Annonaceae", "Piperaceae" and "isolated", with interposition of the Boolean operator "AND", from 2000 to 2019 only for plant extracts, while search for articles on acetogenins had no period filter (accessed between January and July 2019). Therefore, all $LC_{50(90)}$ values are presented in μg/mL to allow comparison of results. In the case of studies investigating several extracts, with different solvents or parts, of the same plant species, we include the results with the smallest LC_{50}. Articles with no data on LC_{50} and LC_{90} were excluded from the study (Figure 1).

3. Larvicidal effects of plant extracts

In this review, 97 complete articles were selected, as described in the selection methods shown in Figure 1. The larvicidal potential of plant extracts from 150 species distributed in 52 botanical families was evaluated on *Ae. aegypti* and *Ae. albopictus*, vectors of recurrent arboviruses in tropical and subtropical countries. Most of the plants whose extracts were tested are from the families Fabaceae (18 species), Asteraceae (15 species), Euphorbiaceae (10 species), Rutaceae (8 species), Cucurbitaceae (7 species), Lamiaceae (6 species) and Annonaceae (6 species). At the same time, almost all plant extracts (138 species) were tested only on *Ae. aegypti* species, while only 12 plants were tested against *Ae. albopictus* larvae (Table 1).

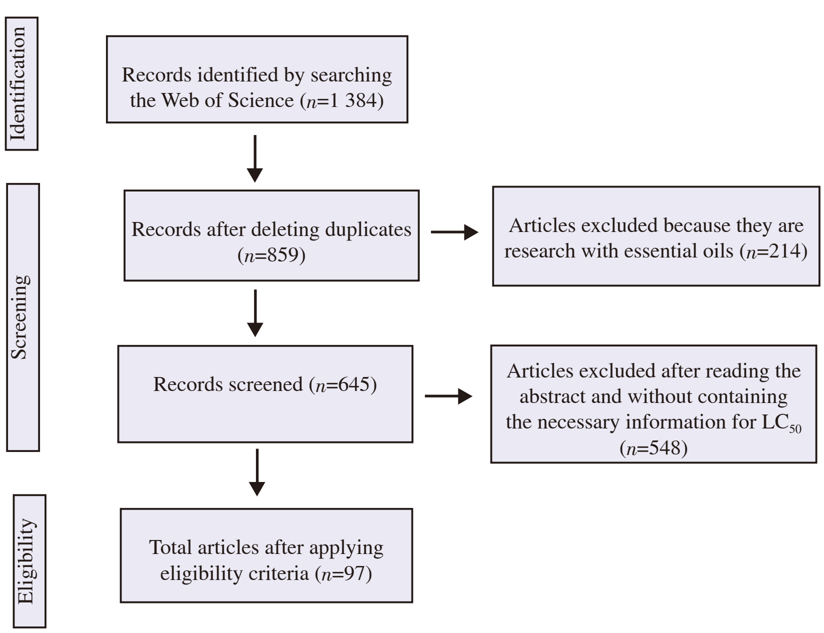


Figure 1. Flowchart with description of the design process of this study.

Table 1. Larvicidal activity of plant extracts on *Aedes aegypti* and *Aedes albopictus* larvae.

Family	Plant	Part of the plant	Solvent used	LC_{50} (μg/mL)	LC_{90} (μg/mL)	*Aedes* species	Larval instar	Reference
Acanthacae	*Andrographis echiodies* (L.) Nees	Leaf	Methanol	93.0	171.81	*Aedes aegypti*	4	[14]
	Andrographis lineata Wallich	Leaf	Distilled water	152.23	241.31	*Aedes aegypti*	4	[15]
	Andrographis paniculata (Burm.f.)	Leaf	Chloroform	99.54	190.10	*Aedes aegypti*	3	[16]
	Argemone mexicana L.	Seed	Petroleum ether	33.12	298.95	*Aedes aegypti*	4	[17]
	Rhinacanthus nasutus Kurz.	Leaf	Methanol	94.43	344.93	*Aedes aegypti*	4	[18]
Actiniopteridaceae	*Actiniopteris radiata* (Sw.) Link.	Leaf	Methanol	67.58	435.33	*Aedes aegypti*	4	[19]
Alangiaceae	*Alangium salvifolium* L. f.	Leaf	Methanol	104.8	269.15	*Aedes aegypti*	4	[20]
Aloaceae	*Aloe fibrosa* Lavranos & L.E. Newton	Leaf	Hexane	50	90	*Aedes aegypti*	3	[21]
	Aloe ngongensis Christian	Leaf	Hexane	110	480	*Aedes aegypti*	3	[21]
	Aloe turkanensis Christian	Leaf	Ethyl acetate	110	190	*Aedes aegypti*	3	[21]
	Aloe vera L.	Leaf	Petroleum ether	300.06	612.96	*Aedes aegypti*	4	[22]
Amaranthaceae	*Achyranthes aspera* L.	Stem	Hexane	57.50	90.84	*Aedes aegypti*	4	[23]
Amaryllidaceae	*Allium sativum* L.	Stem	Hexane	218.35	434.76	*Aedes aegypti*	4	[23]
Anacardiaceae	*Mangifera indica* L.	Leaf	Methanol	8 570	13 770	*Aedes aegypti*	4	[24]
Annonaceae	*Annona crassiflora* Mart.	Root bark	Ethanol	0.71	5.12	*Aedes aegypti*	4	[10]
	Annona glabra L.	Seed	Ethanol	0.06	2.75	*Aedes aegypti*	4	[10]
	Annona muricata L.	Root	Ethanol	42.3	200	*Aedes aegypti*	4	[10]
	Annona squamosa L.	Seed	Ethanol	5.12; 5.26	21.40; 38.37	*Aedes aegypti*; *Aedes albopictus*	4	[10,25]
	Cleistopholis patens (Benth.) Engl. & Diels	Leaf	Methanol	4 410	7 120	*Aedes aegypti*	4	[24]
	Enantia chlorantha Oliv.	Stem bark	Methanol	4 550	6 480	*Aedes aegypti*	4	[24]
Apiaceae	*Trachyspermum ammi* L.	Fruit	Hexane	65.57	108.90	*Aedes aegypti*	4	[23]
Apocynaceae	*Allamanda violacea* Gardner	Leaf	Ethanol	218.9	906.4	*Aedes aegypti*	4	[26]
	Calotropis gigantea L.	Leaf	Ethanol	164.01	353.11	*Aedes aegypti*	4	[27]
	Ervatamia coronaria (Jacq.) Stapf.	Leaf	Benzene	89.59	166.04	*Aedes aegypti*	3	[28]
	Landolphia owariensis P. Beauv.	Leaf	Methanol	3 620	6 110	*Aedes aegypti*	4	[24]
	Nerium oleander L.	Leaf	Methanol	84.09	163.92	*Aedes aegypti*	3 and 4	[29]
Asparagaceae	*Asparagus racemosus* Willd.	Root	Methanol	97.71	179.92	*Aedes aegypti*	3	[30]
	Dracaena loureiri Gagnep	Fruit	Ethanol	224.73; 261.75	367.93; 648.75	*Aedes aegypti*; *Aedes albopictus*	3	[31]
Asteraceae	*Acanthospermum hispidum* DC.	Leaf	Petroleum benzene	15.22	27.75	*Aedes aegypti*	4	[32]
	Acmella oleracea (L.) R. K. Jansen	Leaf	Ethanol; Distilled water	11.41	23.23	*Aedes aegypti*	3	[33]
	Ambrosia arborescens (Mill.)	Leaf	Distilled water	1 844.61	6 043.95	*Aedes aegypti*	3	[34]
	Artemisia annua L.	Seed	Methanol	5.47	177.01	*Aedes aegypti*	3 and 4	[35]
	Artemisia herba-alba Asso	Leaf	Distilled water	117.18	227.63	*Aedes aegypti*	4	[36]
	Artemisia nilagirica (Clarke) Pamp.	Leaf	Methanol	470.74	892.01	*Aedes aegypti*	4	[37]
	Blumea mollis (D. Don) Merr.	Leaf	Methanol	273.68	547.21	*Aedes aegypti*	4	[38]
	Chrysanthemum sp.	Leaf	Ethanol	104.76	260.02	*Aedes aegypti*	4	[39]
	Eclipta alba (L.) Hassk	Leaf	Methanol	127.64	245.73	*Aedes aegypti*	3	[40]
	Parthenium hysterophorus L.	Root	Hexane	432.38	1 118.5	*Aedes aegypti*	4	[7]
	Senecio biafrae L.	Whole plant	Methanol	4 730	7 620	*Aedes aegypti*	4	[24]
	Senecio laetus Edgew.	Root	Methanol	22.3	144.67	*Aedes aegypti*	4	[41]
	Solidago canadenses L.	Leaf	Petroleum ether	15.98	61.16	*Aedes aegypti*	4	[42]
	Spilanthus mauritiana Rich	Leaf	Ethyl acetate	14.10	33.08	*Aedes aegypti*	4	[42]
	Tagetes erecta L.	Leaf	Methanol	275.80	535.95	*Aedes aegypti*	4	[38]
Balsaminaceae	*Impatiens balsamina* L.	Leaf	Methanol	119.68	210.14	*Aedes aegypti*	3	[43]
Bignoniaceae	*Tecoma stans* L.	Leaf	Petroleum ether	55.41	109.33	*Aedes aegypti*	3 and 4	[29]
Calophyllaceae	*Calophyllum mucigerum* Guttiferae	Stem bark	Hexane	87.9	256.3	*Aedes aegypti*	3	[44]
Cannaceae	*Canna indica* L.	Leaf	Methanol	3 840	6 410	*Aedes aegypti*	4	[24]
Caricaceae	*Carica papaya* L.	Seed	Ethanol	107	150	*Aedes aegypti*	3	[45]
Combretaceae	*Terminalia chebula* Retz.	Seed	Methanol	138	220	*Aedes aegypti*	4	[46]
Convolvulaceae	*Ipomoea cairica* (L.) Sweet	Leaf	Methanol	12.7; 20.5	62.3; 625	*Aedes aegypti*; *Aedes albopictus*	3	[47]
	Merremia emarginata (Burm. F.) Hall.	Leaf	Distilled water	157.87	301.63	*Aedes aegypti*	3	[48]
Costaceae	*Costus afer* K. Schum	Leaf	Methanol	8 250	13 540	*Aedes aegypti*	4	[24]
Cucurbitaceae	*Citrullus colocynthis* (L.) Schrad.	Seed	Petroleum ether	52.62	153.31	*Aedes aegypti*	4	[17]
	Citrullus vulgaris Schrad.	Leaf	Benzene	42.76	85.76	*Aedes aegypti*	3	[49]
	Coccinia indica Wight & Arn.	Leaf	Methanol	158	341	*Aedes aegypti*	4	[50]

Table 1. Continued.

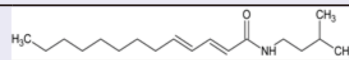
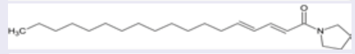
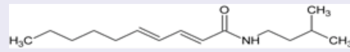
Family	Plant	Part of the plant	Solvent used	LC_{50} (μg/mL)	LC_{90} (μg/mL)	*Aedes* species	Larval instar	Reference
	Cucumis sativus L.	Leaf	Methanol	492.73	1 824.20	*Aedes aegypti*	4	[51]
	Melothria maderaspatana (L.) Cogn	Leaf	Distilled water	0.51	1.08	*Aedes aegypti*	4	[52]
	Momordica charantia L.	Leaf	Methanol	199.14	780.10	*Aedes aegypti*	4	[51]
	Trichosanthes anguina L.	Leaf	Acetone	554.20	2 235.34	*Aedes aegypti*	4	[51]
Cupressaceae	*Cryptomeria japonica* D. Don	Heartwood-type	Methanol	11.5; 15.8	23.4; 62.4	*Aedes aegypti*; *Aedes albopictus*	4	[53]
	Cunninghamia konishii Hayata	Wood	Ethanol	240.0; >400.0	>400.0; >400.0	*Aedes aegypti*; *Aedes albopictus*	4	[54]
Cymodoceaceae	*Cymodocea serrulata* R.Br.	Leaf	Ethanol	42.9	76.3	*Aedes aegypti*	4	[55]
	Halodule pinifolia Milki	Root	Ethanol	22	62.4	*Aedes aegypti*	4	[55]
Euphorbiaceae	*Acalypha alnifolia* Klein ex Willd.	Leaf	Methanol	128.55	381.67	*Aedes aegypti*	4	[56]
	Cnidoscolus phyllacanthus (Müll. Arg.) Fern. Casas	Stem	Ethanol	246	2 145	*Aedes aegypti*	3	[57]
	Euphorbia antiquorum L.	Latex	Chloroform	82.17	201.03	*Aedes aegypti*	3	[58]
	Euphorbia hirta L.	Stem bark and leaves	Petroleum ether	272.36	703.76	*Aedes aegypti*	4	[59]
	Euphorbia rothiana Spreng.	Leaf	Distilled water	8.28	40.19	*Aedes aegypti*	3	[60]
	Euphorbia tirucalli L.	Stem bark and leaves	Petroleum ether	4.25	13.14	*Aedes aegypti*	4	[59]
	Excoecaria agallocha L.	Leaf	Methanol	41.74	123.61	*Aedes aegypti*	3	[61]
	Jatropha curcas L.	Stem bark and leaves	Petroleum ether	8.79	35.39	*Aedes aegypti*	4	[59]
	Pedilanthus tithymaloides (L.) Poit.	Stem bark and leaves	Petroleum ether	55.26	256.77	*Aedes aegypti*	4	[59]
	Ricinus communis L.	Leaf	Hexane	64.26	140.18	*Aedes aegypti*	4	[23]
Fabaceae	*Abrus precatorius* L.	Seed	Methanol	850	1 350	*Aedes aegypti*	4	[24]
	Acacia nilotica (L.) Willd.	Leaf	Petroleum ether	70.42	338.10	*Aedes aegypti*	4	[17]
	Anadenanthera macrocarpa (Benth.) Brenan	Seed	Distilled water	430	710	*Aedes aegypti*	3	[62]
	Bauhinia acuminata L.	Leaf	Distilled water	226.02	428.52	*Aedes aegypti*	3	[63]
Family	*Caesalpinia pulcherrima* (Linn.) Swartz.	Leaf	Benzene	136.36	272.15	*Aedes aegypti*	3	[28]
	Cassia fistula L.	Fruit	Distilled water	1 948	9 172	*Aedes albopictus*	4	[64]
	Cassia occidentalis L.	Leaf	Hexane	74.67	202.35	*Aedes aegypti*	4	[23]
	Clitoria ternatea L.	Seed	Methanol	195.0	599.2	*Aedes aegypti*	4	[65]
	Dalbergia oliveri Gamble	Heartwood	Hexane	153.7	5 048.5	*Aedes aegypti*	3	[66]
	Derris sp.	Root	Ethanol	4.77	8.54	*Aedes aegypti*	4	[10]
	Dioclea megacarpa Rolfe	Seed	Distilled water	6 680	9 750	*Aedes aegypti*	3	[62]
	Enterolobium contortisiliquum (Vell.) Morong	Seed	Distilled water	2 390	3 790	*Aedes aegypti*	3	[62]
	Erythrina indica Lam.	Leaf	Methanol	75.13	134.31	*Aedes aegypti*	3	[67]
	Erythrina mulungu Mart.	Stem bark	Ethanol	36.9	67.9	*Aedes aegypti*	4	[10]
	Ormosia arborea (Vell.) Harms	Seed	Ethanol	111	194	*Aedes aegypti*	3	[68]
	Piptadenia moniliformis Benth	Seed	Distilled water	9 060	13 030	*Aedes aegypti*	3	[62]
	Pterodon polygalaeflorus Benth.	Seed	Ethanol	20.01	35.7	*Aedes aegypti*	4	[10]
	Zornia diphylla (L.) Pers.	Leaf	Distilled water	64.97	126.66	*Aedes albopictus*	3	[69]
Hydrocharitaceae	*Thalasia testudinum* Banks ex Koing	Leaf	Ethanol	44.8	81.2	*Aedes aegypti*	4	[55]
Hypericaceae	*Hypericum japonicum* Thunb.	Whole plant	Methanol	7.37	11.59	*Aedes aegypti*	4	[70]
Lamiaceae	*Hyptis suaveolens* Poit.	Leaf	Petroleum ether	64.49	139.29	*Aedes aegypti*	3 and 4	[29]
	Leucas aspera Willd	Whole plant	Methanol	3.05	8.26	*Aedes aegypti*	4	[71]
	Ocimum canum Sims.	Leaf	Methanol	43.33	61.25	*Aedes aegypti*	4	[72]
	Ocimum sanctum L.	Leaf	Acetone	81.56	541.80	*Aedes aegypti*	4	[18]
	Orthosiphon thymiflorus (Roth) Sleesen.	Leaf	Methanol	149.96	426.16	*Aedes aegypti*	3	[73]
	Plectranthus amboinicus (Lour.) Spreng	Leaf	Methanol	62.41	176.63	*Aedes aegypti*	4	[74]
Lycopodiaceae	*Lycopodium clavatum* L.	Leaf	Methanol	960.27	1 131.97	*Aedes aegypti*	4	[19]

Table 1. Continued.

Family	Plant	Part of the plant	Solvent used	LC_{50} (μg/mL)	LC_{90} (μg/mL)	*Aedes* species	Larval instar	Reference
Malvaceae	*Abutilon indicum* (L.) Sweet	Stem	Hexane	183.61	470.48	*Aedes aegypti*	4	[23]
	Sida acuta Burm. F.	Leaf	Methanol	42.8	78.87	*Aedes aegypti*	3	[75]
Meliaceae	*Aglaia elaeagnoidea* (Juss.) Benth.	Seed	Distilled water	148.5	317.70	*Aedes aegypti*	3	[76]
	Guarea kunthiana A. Juss.	Whole plant	Ethanol	169.93	496.11	*Aedes aegypti*	3	[77]
Menispermaceae	*Dioscoreophyllum cumminsii* L.	Leaf	Methanol	4 520	7 480	*Aedes aegypti*	4	[24]
Moraceae	*Artocarpus altilis* (Parkinson) Fosberg	Stem	Methanol	6 380	10 330	*Aedes aegypti*	4	[24]
	Artocarpus blancoi (Elm.) Merr.	Leaf	Ethanol	411	970	*Aedes aegypti*	4	[78]
Myristicaceae	*Knema attenuata* (Hook. f. & Thomson) Warb.	Seed	Ethanol	159.18	342.10	*Aedes albopictus*	3 and 4	[79]
Myrtaceae	*Eugenia jambolana* Lam.	Leaf	Petroleum ether	40.80	83.28	*Aedes aegypti*	4	[42]
Oleaceae	*Nyctanthes arbor*-tristis L.	Leaf	Chloroform	526.3	1 669.7	*Aedes aegypti*	4	[65]
Orchidaceae	*Habenaria plantaginea* Lindl.	Leaf	Distilled water	111.99; 136.56	216.24; 265.53	*Aedes aegypti*; *Aedes albopictus*	3	[80]
Papaveraceae	*Argemone mexicana* L.	Leaf	Petroleum ether	48.99	189.10	*Aedes aegypti*	4	[17]
Pedaliaceae	*Pedalium murex* L.	Seed	Distilled water	124.7	233.89	*Aedes aegypti*	4	[81]
Phyllanthaceae	*Cleistanthus collinus* Roxb.	Leaf	Ethyl acetate	560.41	2 669.86	*Aedes aegypti*	3	[82]
	Phyllanthus amarus Schumach.	Leaf	Petroleum ether	90.92	384.19	*Aedes aegypti*	4	[59]
	Phyllanthus emblica L.	Fruit	Hexane	298.93	454.32	*Aedes aegypti*	4	[23]
Pinaceae	*Pinus caribaea* Morelet	Leaf	Acetone	92	760	*Aedes aegypti*	3 and 4	[83]
Piperaceae	*Piper aduncum* L.	Leaf	Chloroform	192	346	*Aedes aegypti*	3	[68]
	Piper hispidum Sw.	Leaf	Ethanol	169	474	*Aedes aegypti*	3	[68]
	Piper longum L.	Fruit	Ethanol	0.248	0.605	*Aedes aegypti*	4	[11]
	Piper nigrum L.	Fruit	Ethanol	0.405	0.801	*Aedes aegypti*	4	[11]
Plantaginaceae	*Scoparia dulcis* L.	Aerial part	Distilled water	3 383	5 757	*Aedes aegypti*	ND	[84]
Plumbaginaceae	*Plumbago zeylanica* L.	Root	Ethanol	27.40	72.06	*Aedes aegypti*	4	[85]
Polygalaceae	*Polygala arvensis* Willd	Leaf	Methanol	58.21	208.45	*Aedes aegypti*	3	[86]
Pteridaceae	*Adiantum caudatum* L.	Leaf	Methanol	95.89	640.21	*Aedes aegypti*	4	[19]
	Cheilanthes swartzii Webb. et Benth.	Leaf	Methanol	271.46	734.13	*Aedes aegypti*	4	[19]
	Hemionitis arifolia Burm.	Leaf	Methanol	630.54	812.62	*Aedes aegypti*	4	[19]
Rubiaceae	*Ixora coccinea* L.	Flower	Ethanol	139.6	400.6	*Aedes aegypti*	4	[26]
	Morinda citrifolia L.	Leaf	Methanol	277.92	568.18	*Aedes aegypti*	3	[87]
	Rubia cordifolia L.	Root	Methanol	3.86	8.28	*Aedes aegypti*	3	[88]
	Spermacoce latifólia Aubl.	Aerial part	Methanol	620	1 250	*Aedes aegypti*	3	[89]
Rutaceae	*Chloroxylon swietenia* DC	Leaf	Ethyl acetate	80.58	200.96	*Aedes aegypti*	4	[38]
	Citrus limetta Risso	Bark	Hexane	96.15	163.27	*Aedes aegypti*	4	[90]
	Citrus sinensis (L.) Osbeck	Fruit bark	Ethanol	436.93	891.63	*Aedes aegypti*	4	[91]
	Clausena lansium (Lour.) Skeel	Seed	Petroleum ether	22.99	89.11	*Aedes albopictus*	4	[92]
	Euodia ridleyi Hochr.	Leaf	Ethyl acetate	149.4	195.6	*Aedes aegypti*	4	[42]
	Euodia rutaecarpa (Juss.) Benth.	Fruit	Ethanol	43.21	105.54 (LC_{95})	*Aedes albopictus*	4	[93]
	Feronia limonia (L.) Swingle	Leaf	Acetone	195.99	468.37	*Aedes aegypti*	4	[94]
	Glycosmis pentaphylla (Retz.) DC.	Leaf	Chloroform	112	31 385	*Aedes aegypti*	4	[95]
Sapotaceae	*Mimusops elengi* L.	Leaf	Distilled water	246.57	638.11	*Aedes albopictus*	4	[96]
Solanaceae	*Cestrum nocturnum* L.	Root	Ethanol	38.50	90.43	*Aedes aegypti*	4	[85]
	Solanum trilobatum L.	Leaf	Acetone	125.87	212.50	*Aedes aegypti*	4	[97]
	Solanum variabile Mart.	Leaf	Ethanol	188	284	*Aedes aegypti*	3	[68]
	Solanum xanthocarpum Schrad. & Wendl.	Fruit	Methanol	253.18	435.16	*Aedes aegypti*	3	[98]
	Withania somnifera (L.) Dunal	Leaf	Petroleum ether	89.19	281.34	*Aedes aegypti*	4	[17]
Turneraceae	*Turnera ulmifolia* L.	Leaf	Ethanol	242	899	*Aedes aegypti*	3	[68]
Zingiberaceae	*Curcuma longa* L.	Rhizome	Methanol	2 620	4 450	*Aedes aegypti*	4	[24]
	Curcuma raktakanda Mangaly & Sabu	Leaf	Petroleum ether	15.00	58.75	*Aedes aegypti*	4	[99]
	Zingiber officinalis L.	Stem	Hexane	55.00	129.41	*Aedes aegypti*	4	[23]
	Zingiber zerumbet (L.) Smith	Rhizome	Dichloromethane	89.8	170.5	*Aedes aegypti*	3	[100]

LC_{50}: concentration that kills 50% of the exposed larvae (in μg/mL). LC_{90}: concentration that kills 90% of the exposed larvae (in μg/mL). ND: Not determined.

Table 2. Larvicidal activity of isolated Piperaceae compounds against *Aedes aegypti*.

Compound	Plant	Chemical structure	Molecular formula	LC_{50}	Reference
Pipilyasine	*Piper nigrum* L.		$C_{18}H_{33}NO$	28.0	[118]
Pipzubedine	*Piper nigrum* L.		$C_{22}H_{41}NO$	22.0	[118]
Pipyaqubine	*Piper nigrum* L.		$C_{22}H_{39}NO$	31.0	[118]
Pellitorine	*Piper nigrum* L.		$C_{15}H_{27}NO$	20.0	[118]
Pipericine	*Piper nigrum* L.		$C_{22}H_{41}NO$	25.0	[118]
Piperine	*Piper nigrum* L.		$C_{17}H_{19}NO_3$	10.0	[118]
1-butyl-3,4-methylenedioxybenzene	*Piper corcovadensis* (Miq.) C. DC.		$C_{11}H_{14}O_2$	22.1	[119]
Terpinolene	*Piper corcovadensis* (Miq.) C. DC.		$C_{10}H_{16}$	31.2	[119]

LC_{50}: concentration that kills 50% of the exposed larvae (in μg/mL).

Regarding the toxicity of the extracts of these plants on *Aedes* larvae, only 21 plants out of 150 investigated showed noteworthy larvicidal effect, with LC_{50} values below 20 μg/mL. Among these plants, the Annonaceae family presented the best performance, in which 3 of the 6 studied species had LC_{50} lower than 10 μg/mL (Table 1). *A. glabra* and *A. crassiflora* presented LC_{50} values of 0.06 μg/mL and 0.71 μg/mL, respectively[10].

Two of the Piperaceae families investigated, *Piper* (*P.*) *longum* L. and *P. nigrum* L., showed strong action, with LC_{50} values of 0.248 μg/mL and 0.405 μg/mL, respectively, against *Ae. aegypti* larvae[11]. According to Simas *et al.*[12], fractionation of *P. nigrum* ethanol extract, biomonitored by assays with pyrethroid-resistant *Ae. aegypti* larvae, yielded isolation of the larvicidal amides piperolein-A and piperine. With respect to LC_{50} values, the ethanol extract of *P. nigrum* (0.405 μg/mL) (Table 1) was the most toxic, in comparison with the isolated compounds pipericine (25 μg/mL) and piperine (10 μg/mL) (Table 2). In tests with substances derived from *P. longum*, no activity was observed of piperettine, piperine, or piperlongumine[13]. It seems that extracts are better larvicides than isolated constituents, probably due to the synergism among several constituents of the extract.

4. Annonaceae for vector control

Annonaceae is a family of plants widely adapted to rainforests, with 2 500 identified species distributed in 135 genera worldwide[101,102]. In Brazil, there are 29 genera and 385 species in the Amazon and Atlantic rainforests, denoting richness and diversity. Anonaceae plants are economically important because their fruits are edible, eaten fresh and/or used in the production of juices and ice cream, such as ata (*A. squamosa* L.), graviola (*A. muricata* L.) and biribá (*A. mucosa* Jacq.)[103].

The potential for biological activities of substances derived from *A. mucosa* has been investigated and antimicrobial, larvicidal, insecticidal, repellent and antitumor activities have been confirmed[104-110]. Acetogenins (ACGs) with antileishmanial properties[111] and larvicides[8] were obtained from *A. muricata* seeds.

In biosynthetic terms, ACGs are compounds derived from long fatty acid chains. In long aliphatic chains (between 32 and 34 carbon atoms) of ACGs, one, two or three tetrahydrofuran (THF) or tetrahydropyran rings can be found, plus a terminal, saturated or unsaturated γ-lactone ring[112].

A. squamosa seed extract showed adulticidal, larvicidal and ovicidal effects and deterred oviposition of *Ae. albopictus*[25]. The ethanol extract of *A. muricata* and its major component, annonacin, had significant larvicidal action on *Ae. aegypti* and *Ae. albopictus* populations, through enzyme inhibitory effect[8].

The larvicidal activity of 50 acetogenins isolated from plants of the Annonaceae family on *Aedes* was investigated, and only the potential of annonacin was verified against *Ae. albopictus*. All other acetogenins were tested only on *Ae. aegypti* (Table 3). Among the acetogenins tested, 24 are classified as mono-THF because they have only one tetrahydrofuran ring, and 26 are bis-THF because they have two tetrahydrofuran rings[112] (Table 3). Structural representations of acetogenins are available in supplementary Table 1.

Regarding the larvicidal potential of ACGs mono-THF, 9 out of 24 ACGs tested presented LC_{50} values below 10 μg/mL, while LC_{50} above 50 μg/mL. In the ACGs bis-THF, 19 out of 26 had LC_{50} below 10 μg/mL and only 2 ACGs had LC_{50} above 50 μg/mL (Table 3). Hence, there is a positive correlation between the number of THF rings and the larvicidal potential of ACGs.

Among the 14 most active ACGs on *Ae. aegypti* are: bullatacin (LC_{50}=0.1 μg/mL), rolliniastatin-1 (LC_{100}=0.2 μg/mL), trilobin (LC_{50}=0.67 μg/mL), purpureacin-2 (LC_{50}=1 μg/mL), asiminacin

Table 3. Larvicidal action of acetogenins against *Aedes aegypti* and *Aedes albopictus*.

ACG	Plant	Molecular formula	*Aedes* species (Instar)	LC_{50}/LC_{90} (μg/mL)	Reference
Acetogenins mono-THF					
Annonacin	*Annona muricata* L.	$C_{35}H_{64}O_7$	*Aedes aegypti* (3 days); *Aedes albopictus* (4 days)	2.65/4.83; 8.34/16.3	[8]
Annonacin A	*Annona muricata* L.	$C_{35}H_{64}O_7$	*Aedes aegypti* (4 days)	10.8	[113]
Annopentocin A	*Annona mucosa* Jacq.	$C_{35}H_{64}O_8$	*Aedes aegypti* (4 days)	>50	[113]
Annopentocin B	*Annona mucosa* Jacq.	$C_{35}H_{64}O_8$	*Aedes aegypti* (4 days)	>50	[113]
Annopentocin C	*Annona mucosa* Jacq.	$C_{35}H_{64}O_8$	*Aedes aegypti* (4 days)	>50	[113]
Disepalin	*Disepalun anomalum*	$C_{39}H_{70}O_8$	*Aedes aegypti* (4 days)	27.4/82	[115]
Giganenin	*Goniothalamus giganteus* Hook. f. eThomas	$C_{37}H_{66}O_6$	*Aedes aegypti* (4 days)	7.8	[113]
Gigantetrocin	*Goniothalamus giganteus* Hook. f. e Thomas	$C_{35}H_{64}O_7$	*Aedes aegypti* (4 days)	18.5	[113]
Gigantetrocin A	*Goniothalamus giganteus* Hook. f. e Thomas	$C_{35}H_{64}O_7$	*Aedes aegypti* (4 days)	10.4	[113]
Goniothalamicin B	*Goniothalamus giganteus* Hook. f. e Thomas	$C_{35}H_{64}O_7$	*Aedes aegypti* (4 days)	13.3	[113]
Longicoricin	*Asimina longifolia* Kral	$C_{37}H_{68}O_6$	*Aedes aegypti* (4 days)	58	[113]
Longifolicin	*Asimina longifolia* Kral	$C_{35}H_{64}O_6$	*Aedes aegypti* (4 days)	249	[113]
Rollinecin A	*Annona mucosa* Jacq.	$C_{37}H_{68}O_7$	*Aedes aegypti* (4 days)	>50	[113]
Rollinecin B	*Annona mucosa* Jacq.	$C_{37}H_{68}O_7$	*Aedes aegypti* (4 days)	>50	[113]
Annonacin 4-OAc	*Annona muricata* L.	$C_{38}H_{68}O_8$	*Aedes aegypti* (4 days)	6.2	[113]
Xylomaticin 4-OAc	*Annona muricata* L.	$C_{39}H_{70}O_8$	*Aedes aegypti* (4 days)	6.2	[113]
Gigantetrocinone	*Goniothalamus giganteus* Hook. f. e Thomas	$C_{35}H_{64}O_7$	*Aedes aegypti* (4 days)	2.2	[113]
Gigantetroneninone	*Goniothalamus giganteus* Hook. f. e Thomas	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	8.3	[113]
cis-Gigantrionenin	*Goniothalamus giganteus* Hook. f. e Thomas	$C_{37}H_{66}O_6$	*Aedes aegypti* (4 days)	8.6	[113]
Gigantrionenin	*Goniothalamus giganteus* Hook. f. e Thomas	$C_{37}H_{66}O_6$	*Aedes aegypti* (4 days)	5	[113]
Muricatetrocin C	*Annona mucosa* Jacq.	$C_{35}H_{64}O_7$	*Aedes aegypti* (4 days)	>50	[113]
Muricatretrocin B	*Annona mucosa* Jacq.	$C_{35}H_{64}O_7$	*Aedes aegypti* (4 days)	2.2	[113]
Murihexocin A	*Annona muricata* L.	$C_{35}H_{64}O_9$	*Aedes aegypti* (4 days)	>50	[113]
Murihexocin B	*Annona muricata* L.	$C_{35}H_{64}O_9$	*Aedes aegypti* (4 days)	>50	[113]
Acetogenins bis-THF					
10-OH Asimicin	*Asimina triloba* Dunal	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	15.2	[113]
12-OH Bullatacin A	*Annona bullata* Rich.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	8	[113]
12-OH Bullatacin B	*Annona bullata* Rich.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	8	[113]
Bullatetrocin	*Annona bullata* Rich.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	6.2	[113]
Cherimoline	*Annona purpurea* Moc & Sessé ex Dunal	$C_{37}H_{66}O_8$	*Aedes aegypti* (2 days)	2 (LC_{100})	[116]
Purpureacin-2	*Annona purpurea* Moc & Sessé ex Dunal	$C_{37}H_{66}O_8$	*Aedes aegypti* (2 days)	1 (LC_{100})	[116]
Rollidecin A	*Annona mucosa* Jacq.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	11.2	[113]
Rollidecin B	*Annona mucosa* Jacq.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	>50	[113]
Rollitacin	*Annona mucosa* Jacq.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	4.7	[113]
Squamocin	*Annona squamosa* L.	$C_{37}H_{66}O_7$	*Aedes aegypti* (3 days)	6.4	[117]
Rolliniastatin-1	*Annona purpurea* Moc & Sessé ex Dunal	$C_{37}H_{66}O_7$	*Aedes aegypti* (2 days)	0.2 (LC_{100})	[116]
Trilobacin	*Asimina triloba* Dunal	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	1.6	[113]
Trilobacinone	*Asimina triloba* Dunal	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	10.4	[113]
Trilobin	*Asimina triloba* Dunal	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	0.67	[113]
Asimicin	*Asimina triloba* Dunal	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	2.7	[113]
Asiminacin	*Asimina triloba* Dunal	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	1.6	[113]
Bullatacin	*Annona bullata* Rich.	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	0.1	[113]
Longimicin B	*Asimina longifolia* Kral	$C_{35}H_{62}O_7$	*Aedes aegypti* (4 days)	27.3	[113]
Longimicin C	*Asimina longifolia* Kral	$C_{35}H_{62}O_7$	*Aedes aegypti* (4 days)	65.7	[113]
Longimicin D	*Asimina longifolia* Kral	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	11.5	[113]
Motrilin	*Annona mucosa* Jacq.	$C_{37}H_{66}O_7$	*Aedes aegypti* (4 days)	4.7	[113]
Bullatalicin	*Annona mucosa* Jacq.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	9	[113]
Mucosin	*Annona mucosa* Jacq.	$C_{20}H_{32}O_2$	*Aedes aegypti* (4 days)	2.1	[113]
Purpureacin-1	*Annona purpurea* Moc & Sessé ex Dunal	$C_{37}H_{66}O_8$	*Aedes aegypti* (2 days)	2 (LC_{100})	[116]
cis-Sylvaticin	*Annona mucosa* Jacq.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	6	[113]
Sylvaticin	*Annona mucosa* Jacq.	$C_{37}H_{66}O_8$	*Aedes aegypti* (4 days)	1.6	[113]

LC_{50}: concentration that kills 50% of the exposed larvae (in μg/mL). LC_{90}: concentration that kills 90% of the exposed larvae (in μg/mL). LC_{100}: concentration that kills 100% of the exposed larvae (in μg/mL).

(LC_{50}=1.6 μg/mL), sylvaticin (LC_{50}=1.6 μg/mL), trilobacin (LC_{50}=1.6 μg/mL), asimicin (LC_{50}=1.7 μg/mL), cherimoline (LC_{100}=2 μg/mL), purpureacin-1 (LC_{100}=2 μg/mL), mucosin (LC_{50}=2.1 μg/mL), muricatretrocin B (LC_{50}=2.2 μg/mL), gigantetrocinone (LC_{50}=2.2 μg/mL) and annonacin (LC_{50}=2.65 μg/mL) (Table 3).

The ethanol extract of *A. muricata* root presented LC_{50} of 42.3 μg/mL against *Ae. aegypti*[10] while isolated compounds had lower LC_{50} values, such as annonacin, annonacin A, annonacin 4-OAc, with LC_{50} values of 2.65, 10.80 and 6.20 μg/mL, respectively[8,113].

There is no doubt about the potential of natural products extracted from plants for the control of mosquito vectors of human diseases such as arboviruses. However, despite the vast literature confirming the larvicidal action of plant extracts and their isolated constituents, no commercial plant-based larvicide is available at this time[114].

5. Piperaceae for vector control

The Piperaceae family comprises 4 000 species of plants that are distributed in five genera: *Manekia*, *Peperomia*, *Piper*, *Verhuellia* and *Zippelia*. They are found in tropical countries and often used in traditional medicine. In Brazil, peppers such as *P. cernuum* (bat pepper) are used to control abdominal colic[119]. The performance of natural Piperaceae products has been demonstrated on *Ae. aegypti* larvae[68] and their high lethality has been shown to be a promising source for the alternative control of these mosquitoes[11].

The larvicidal activity of 8 compounds isolated from plants of the genus *Piper* of the family Piperaceae were tested against *Ae. aegypti* larvae in the fourth instar and presented LC_{50} below 32 μg/mL (Table 2).

6. Conclusions and perspectives

This review shows the abundance of research on the effect of natural products of plant origin on *Aedes* larvae, especially in relation to the species *Ae. aegypti*, the main vector of arboviruses such as dengue, Zika and chikungunya in Brazil. However, few studies have reported the effect of these plants against *Ae. albopictus*, a secondary vector of these diseases.

The two plant families whose extracts were most active on *Aedes* were found to be Annonaceae and Piperaceae, plants whose fruits are used for food and therefore grown for this purpose (*e.g.*, *A. muricata*, *A. mucosa*, *P. nigrum* and *P. longum*). This suggests the possible economic feasibility of using these plants to produce commercial insecticides. Acetogenins, isolated from Annonaceae, have shown significant larvicidal activity, so further studies should be performed to verify the viability of these substances as commercial larvicides. The synthesis of acetogenins with high larvicidal activity is already known, such as annonacin, muricatetrocin and sylvatacin, among many others[120,121], all of which can be used for production of these compounds.

We believe it is economically feasible to produce environmentally safe natural larvicides with low lethality to non-target organisms from plant extracts of the Annonaceae or Piperaceae family, including through organic synthesis of the most active acetogenins, which are effective in controlling mosquito vectors of human diseases such as *Ae. aegypti* and *Ae. albopictus*.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

AMR and SMM designed the study. VEPM suggested that AMR investigate the larvicidal activity of plant extracts, while SMM suggested the introduction of the larvicidal action of acetogenins. All three authors discussed the manuscript. AMR and SMM led the writing of the manuscript with the support of VEPM. VEPM critically reviewed the approach regarding arboviruses and mosquito vectors. All authors discussed the results and contributed to comments on the manuscript. The whole manuscript was read and approved by all authors.

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