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INTERFACES CIENTÍFICAS

PIPER PLANTS AS AN ALTERNATIVE TO THE CONTROL OF *AEDES AEGYPTI* AND *AEDES ALBOPICTUS*: AN INTEGRATIVE REVIEW

PLANTAS DO GÊNERO *PIPER* COMO ALTERNATIVA PARA O CONTROLE DE *AEDES AEGYPTI* E *AEDES ALBOPICTUS*: UMA REVISÃO INTEGRATIVA

PLANTAS DEL GÉNERO *PIPER* COMO ALTERNATIVA PARA EL CONTROL DE *AEDES AEGYPTI* Y *AEDES ALBOPICTUS*: UNA REVISIÓN INTEGRATIVA

Marcos Martins Lima[1]
Tamires de Moura Lima[2]
Kaio da Silva Bandeira[3]
Rafael Costa Leite[4]
João Gustavo Mendes Rodrigues[5]
Guilherme Silva Miranda[6]

ABSTRACT

Aedes aegypti and *A. albopictus* are the main vectors of severe arboviruses. Plant-derived natural products may represent an important source of secondary metabolites for controlling these vectors. Therefore, we performed an integrative literature review on the effectiveness of *Piper* spp. as natural alternative to the control of *A. aegypti* and *A. albopictus* in experimental assays. We searched the scientific databases available in PubMed, Scopus, and Google Scholar for articles published between 2002 and 2022. A total of 225 articles were preselected; however, 41 studies were evaluated in detail after applying the exclusion and inclusion criteria. We observed the use of 43 different species of *Piper*, of which *Piper aduncum* (n=9, 21%) was the most commonly used. The plant structures most commonly used in bioassays were the leaves (n = 28; 68%), which were processed as crude extracts (n = 23; 56%) to evaluate the larvicidal effect (n = 36; 88%) on *A. aegypti* (n = 40; 97.5%). The best LC_{50} (lethal concentration capable of killing 50% of the organism of interest) was observed for the extract of *P. hispidum* leaves against larvae. The secondary metabolites frequently found in natural products derived from *Piper* were: -selinene, -pinene, pelitorin, E-caryophyllene, linalool, and germacrene D. Thus, this review synthesises knowledge generated over 20 years to confirm the potential of *Piper* in controlling *A. aegypti* and *A. albopictus*. Our data indicate that insecticidal molecules were found in *Piper* plants with great potential to become new commercial products to control populations of these vectors.

KEYWORDS

Arboviruses. *Piper. Aedes*. Essential Oil.

RESUMO

Aedes aegypti e *A. albopictus* são os principais vetores de arboviroses para a população humana. Produtos naturais derivados de plantas podem representar uma importante fonte de metabólitos secundários para o controle desses vetores. Portanto, realizamos uma revisão de literatura integrativa sobre a eficácia de *Piper* spp. como alternativa natural para o controle de *A. aegypti* e *A. albopictus* em ensaios experimentais. Pesquisamos artigos publicados entre 2002 e 2022 nas bases de dados científicas disponíveis no PubMed, Scopus e Google Scholar. Foram pré-selecionados 225 artigos; contudo, 41 estudos foram avaliados detalhadamente após aplicação dos critérios de exclusão e inclusão. Observamos o uso de 43 espécies diferentes de *Piper*, das quais *Piper aduncum* (n=9, 21%) foi a mais utilizada. As estruturas vegetais mais utilizadas nos bioensaios foram as folhas (n = 28; 68%), que foram processadas como extratos brutos (n = 23; 56%) para avaliar o efeito larvicida (n = 36; 88%) sobre *A. aegypti* (n = 40; 97,5%). A melhor CL_{50} (concentração letal capaz de matar 50% do organismo de interesse) foi observada para o extrato de folhas de *P. hispidum* contra larvas. Os metabólitos secundários frequentemente encontrados em produtos naturais derivados de *Piper* foram: -selineno, -pineno, pelitorina, E-cariofileno, linalol e germacreno D. Portanto, essa revisão sintetiza o conhecimento gerado ao longo de 20 anos para confirmar o potencial de *Piper* no controle de *A. aegypti* e *A. albopictus*. Nossos dados indicam que moléculas inseticidas foram encontradas em *Piper*, com grande potencial de tornarem-se novos produtos comerciais para controle das populações desses vetores.

PALAVRAS-CHAVE

Arboviroses. *Piper*. *Aedes*. Óleo Essencial.

RESUMEN

Aedes aegypti y *A. albopictus* son los principales vectores de arbovirus para la población humana. Los productos naturales derivados de plantas pueden representar una fuente importante de metabolitos secundarios para el control de estos vectores. Por lo tanto, realizamos una revisión integradora de la literatura sobre la eficacia de *Piper* spp. como alternativa natural para el control de *A. aegypti* y *A. albopictus* en ensayos experimentales. Se buscaron artículos publicados entre 2002 y 2022 en bases de datos científicas disponibles en PubMed, Scopus y Google Scholar. Se preseleccionaron 225 artículos; sin embargo, 41 estudios fueron evaluados en detalle luego de aplicar los criterios de exclusión e inclusión. Observamos el uso de 43 especies diferentes de *Piper*, de las cuales *Piper aduncum* (n=9, 21%) fue la más utilizada. Las estructuras vegetales más utilizadas en los bioensayos fueron las hojas (n = 28; 68%), las cuales fueron procesadas como extractos crudos (n = 23; 56%) para evaluar el efecto larvicida (n = 36; 88%) sobre *A. aegypti* (n = 40; 97,5%). La mejor CL_{50} (concentración letal capaz de matar el 50% del organismo de interés) se observó para el extracto de hoja de *P. hispidum* contra larvas. Los metabolitos secundarios encontrados frecuentemente en los productos naturales derivados de *Piper* fueron: -selineno, -pineno, pelitorina, E-cariofileno, linalool y germacreno D. Por lo tanto, esta revisión sintetiza el conocimiento generado a lo largo de 20 años para confirmar el potencial de *Piper* en el control de *A. aegypti* y *A. albopictus*. Nuestros datos indican que en *Piper* se encontraron moléculas insecticidas, con gran potencial para convertirse en nuevos productos comerciales para controlar poblaciones de estos vectores.

PALABRAS CLAVE

Arbovirosis; *Piper*. *Aedes*. Óleo esencial.

1 INTRODUCTION

Many plant species have been used in traditional medicine for the treatment of various diseases. Among them, the Piperaceae family stands out with approximately two thousand described species, predominantly located in tropical forests (SAMAIN *et al*., 2010). The predominant genus belonging to the Piperaceae family is *Piper* (OLIVEIRA *et al*., 2020) because of its great potential for medicinal purposes (SILVA *et al*., 2017; OLIVEIRA *et al*., 2020). The most relevant biological activities associated with *Piper* are anti-inflammatory, antimicrobial, antiparasitic, and anticancer (SALEHI *et al*., 2019) properties. The secondary metabolites produced by *Piper* plants, such as alkaloids (FACUNDO *et al*., 2012), amides (KAOU *et al*., 2010), and flavonoids (FACUNDO *et al*., 2012; NASCIMENTO *et al*., 2012), are linked with these biological effects. Therefore, we believe that these plants can possibly be widely used to control mosquitoes that transmit arboviruses (arthropod-borne viral infections) such as *Aedes aegypti* (Linnaeus, 1762) and *A. albopictus* (Skuse, 1894). However, few studies have compiled current information on the subject.

The species, *A. aegypti* and *A. albopictus*, are considered predominantly responsible for the transmission of arboviruses, such as Dengue, Zika, Chikungunya, and Yellow Fever (NÃSLUND *et al*., 2021). In recent years, the incidence of arboviruses has increased owing to globalisation, the adaptation of vectors to increasing urbanisation, and environmental changes (ROBERT *et al*., 2020). Thus, there is an urgent need to develop new methods for controlling these vectors, and natural chemical compounds derived from *Piper* may represent an important step in the development of alternative insecticides.

Therefore, the use of *Piper* as a natural alternative for controlling *A. aegypti* and *A. albopictus* over the last 20 years was reviewed in this current study. Information about the main plant structures used, chemical composition of extracts and essential oils, and lethal concentrations of these natural products are discussed.

2 METHODS

2.1 STUDY TYPE AND DATA COLLECTION

This review systematically synthesises the scientific knowledge produced on a given subject over a defined period (SOUZA *et al.*, 2010). Our guiding question was, "How can natural products derived from *Piper* be effective in experimentally controlling the *Aedes* mosquito?". A search was performed of the scientific literature available in the NCBI databases, PubMed, Scopus, and Google Scholar, covering studies published in Portuguese and English between 2002 and 2022. To search these databases, we used the descriptors "*Piper*" and "*Aedes*", in addition to the Boolean operator "and", as a way of linking the two descriptors and restricting the search to the theme of this review (PIZZANI *et al.*, 2012).

After identifying the articles, the selection stage was performed by removing duplicates (the same work indexed in all three databases). The selected articles proceeded to the eligibility stage, and their abstracts, which were original articles that used *A. aegypti* and/or *A. albopictus* as experimental models, were evaluated based on our inclusion criteria. In our final selection, we applied our exclusion criteria and removed review articles, studies that used only isolated compounds or the association of several natural products, repellency tests (because do not induce mortality), and studies that did not evaluate mortality or mention the plant structure used. The final number of articles in the database was evaluated in detail.

2.2 DATA PROCESSING AND ORGANIZATION

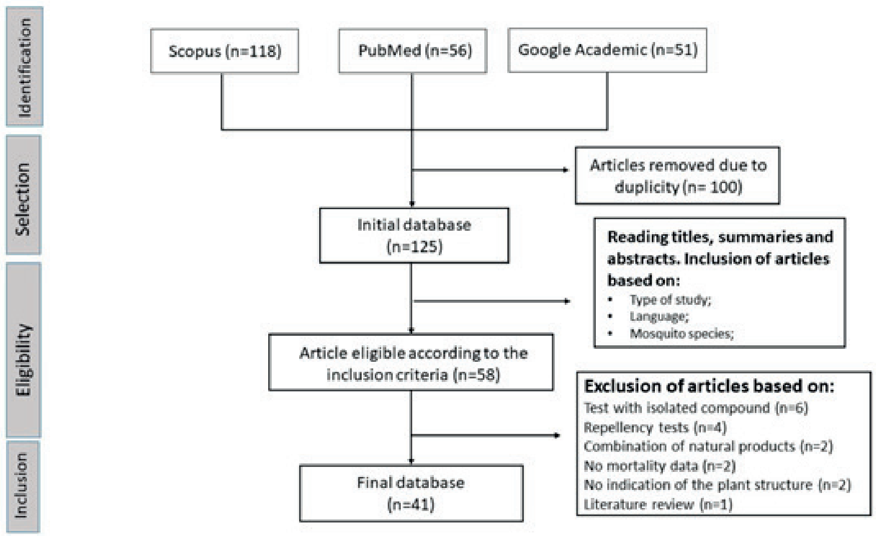
The articles obtained after the selection steps were organised in ascending order of year of publication (2002–2022) using Excel® software. The data extracted from the articles were: authors, year, *Piper* species and plant structure used, type of chemical compounds of natural product obtained (extract or oil), species, ontogenic form of *Aedes* used in bioassays (ovicide, larvicide, pupicide, and adulticide), and LC_{50} values (µg/mL or mg/cm^2).

For each piece of information extracted from the articles, the incidence was calculated and organised into graphs and tables. However, it should be noted that some studies evaluated more than one characteristic (e.g., different plant structures or species of *Piper* in the same study); therefore, some graphs exceed 100%.

3 RESULTS

In total, 225 scientific research articles were found (Scopus = 118, PubMed = 56, and Google Scholar = 51) using our descriptors (Figure 1). Of these, 100 (approximately 45%) were excluded as duplicates (Figure 1). Of the remaining 125 studies, 58 (approximately 47%) were selected based on the inclusion criteria (Figure 1). In the final selection stage, 17 studies were excluded to our exclusion criteria. Finally, 41/58 (approximately 71%) studies were evaluated in detail (Figure 1). Information extracted from the selected studies is presented in Table 1.

Figure 1. Flowchart of the analysis strategies used in this integrative literature review, which covering studies published between 2002 and 2022 that used *Piper* plants in experimental assays with *Aedes aegypti* and *A. albopictus.*



Of the selected articles, 43 different species of *Piper* were used, as demonstrated in **Table 1**. However, the three most commonly used species were *P. aduncum* (n = 9, 21%), *P. nigrum* (n = 8, 19%), and *P. marginatum* (n = 4, 9%) (Figure 2).

Table 1. Data obtained from research articles (2002–2022) that used *Piper* in experimental assays with *Aedes aegypti* and *A. albopictus.*

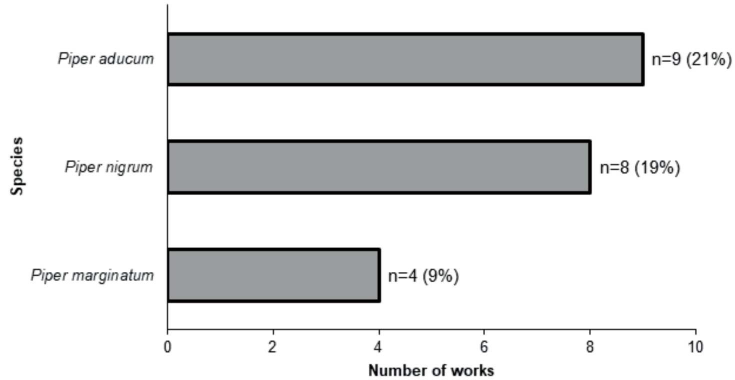
Species	Plant structure	Product obtained	Species of Aedes	Mosquito phase	Authors
P. aduncum	Leaf	Extract	A. aegypti	Adult	Hidayatulfathi *et al.* (2004)
P. longum	Fruit, seed and root	Oil	A. aegypti	Adult	Chaiyasit *et al.* (2006)
P. guineense	Fruit	Extract	A. aegypti	Larva	Oke *et al.* (2007)
P. nigrum	Fruit	Extract	A. aegypti	Larva	Simas *et al.* (2007)

Species	Plant structure	Product obtained	Species of Aedes	Mosquito phase	Authors
P. gaudichaudianum, P. humaytanum P. permucronatum P. hostmannianum	Leaf	Oil	A. aegypti	Larva	Morais *et al*. (2007)
P. marginatum	Leaf, stalk, and inflo-rescence	Oil	A. aegypti	Larva	Autran *et al*. (2009)
P. aduncum P. marginalum P. nigrum	Fruit, leaf, and seed	Oil	A. aegypti	Larva	Costa *et al*. (2010)
P. aduncum	Leaf	Oil	A. aegypti and A. albo-pictus	Adult	Misni *et al*. (2011)
P. nigera	Seed	Extract	A. aegypti	Adult	Nawaz *et al*. (2011)
P. nigrum	Seed	Extract	A. aegypti	Larva	Briones *et al*. (2012)
P. nigrum	Fruit	Extract	A. aegypti	Larva	Grzybowski *et al*. (2013)
P. ovatum	Leaf, root, and stalk	Extract	A. aegypti	Larva	Kanis *et al*. (2013)
P. nigrum	Seed	Extract	A. aegypti	Larva	Gulzar *et al*. (2013)
P. aduncum	Leaf	Oil	A. aegypti	Larva	Oliveira *et al*. (2013)
P. klotzschianum	Root, stalk, leaf, and seed	Oil	A. aegypti	Larva	Nascimento *et al*. (2013)
P. nigrum	Fruit	Extract	A. aegypti	Larva	Santiago *et al*. (2015)
P. arboreum P. marginatum P. aduncum	Leaf	Oil	A. aegypti	Larva	Santana *et al*. (2015)
P. nigrum	Leaf	Extract	A. aegypti	Larva	Lija-Escaline *et al*. (2015)

Species	Plant structure	Product obtained	Species of Aedes	Mosquito phase	Authors
P. augustum *P. corrugatum* *P. curtispicum* *P. darienense* *P. grande* *P. hispidum* *P. jacquemontianum* *P. longispicum* *P. multiplinervium* *P. reticulatum* *P. trigonum*	Leaf	Oil	A. aegypti	Larva	Santana *et al*. (2016)
P. nigrum	Seed	Extract	A. aegypti	Larva	Custódio *et al*. (2016)
P. betle	Leaf	Oil	A. aegypti	Adult	Vasantha-Srinivasan *et al*. (2017)
P. hispidum *P. aduncum*	Leaf	Extract	A. aegypti	Larva	Porto *et al*. (2017)
P. betle	Leaf	Oil	A. aegypti	Larva	Vasantha-Srinivasan *et al*. (2018)
P. ovatum	Root	Extract	A. aegypti	Larva	Kanis *et al*. (2018)
P. ribesioides	Branch	Extract	A. aegypti	Larva	Kumrungsee *et al*. (2018)
P. betle	Leaf	Oil	A. aegypti	Egg, larva, and adult	Martianasari; Hamid (2019)
P. aduncum	Inflorescence	Oil	A. aegypti	Larva	Scalvenzi *et al*. (2019)
P. crocatum	Leaf	Oil	A. aegypti	Larva	Setiawan *et al*. (2019)
P. klotzschianum *P. hispidum* *P. arboreum*	Leaf and stalk	Oil	A. aegypti	Larva	Lima *et al*. (2019)
P. aduncum *P. hispidinervum*	Leaf	Oil	A. aegypti	Larva	Silva *et al*. (2019)

Species	Plant structure	Product obtained	Species of Aedes	Mosquito phase	Authors
P. alatipetiolatum	Leaf	Oil	A. aegypti	Egg, larva, and pupa	Oliveira *et al*. (2020)
P. longum	Leaf	Extract	A. aegypti	Egg and larva	Dey *et al*. (2020)
P. corcovadensis	Root	Extract	A. aegypti	Larva	Fernandez *et al*. (2020)
P. dilatatum *P. hostmannianum*	Leaf	Oil	A. aegypti	Larva	Albuquerque *et al*. (2020)
P. capitarianum	Leaf, stalk, and inflo-rescence	Oil	A. aegypti and A. albo-pictus	Larva	França *et al*. (2021)
P. longum	Leaf	Extract	A. aegypti	Larva	Priya *et al*. (2021)
P. sarmentosum	Leaf	Extract	A. aegypti	Larva	Othman *et al*. (2021)
P. umbellatum	Leaf	Extract	A. aegypti	Larva	Oliveira *et al*. (2021)
P. kadsura	Leaf and stalk	Extract	A. albopictus	Larva	Seo *et al*. (2021)
P. aduncum *P. marginatum* *P. gaudichaudianum* *P. crassinervium* *P. arboreum* *P. hemmendorffii* *P. cernuum* *P. lucaenum* *P. lindbergii* *P. amalago*	Leaf	Oil	A. aegypti	Larva	Pereira-Filho *et al*. (2021)
P. purusanum	Leaf	Oil	A. aegypti and A. albopictus	Egg and larva	Oliveira *et al*. (2022)

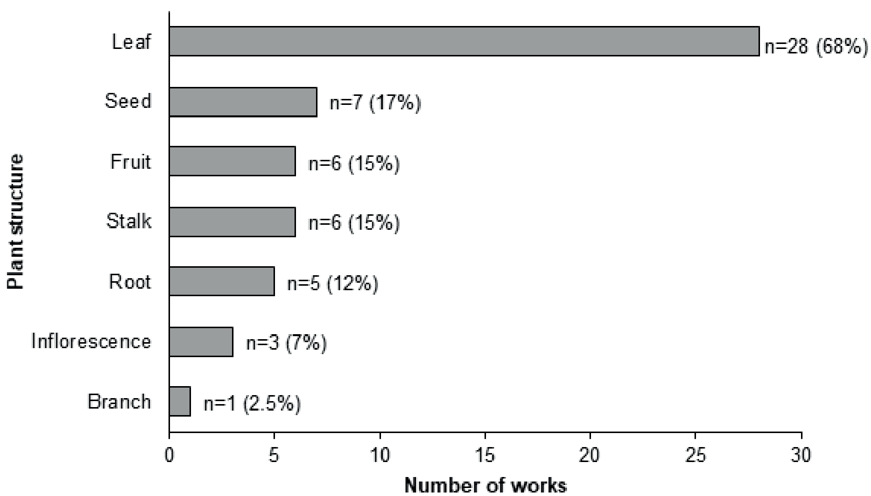
Figure 2. The main *Piper* species used in the research (2002–2022) to control *Aedes aegypti* and *A. albopictus*, which were selected from Scopus, PubMed, and Google Scholar databases.



Source: Research data

The plant structures of *Piper* most commonly used were the leaves (n = 28; 68%), followed by seeds (n = 7; 17%), fruit (n = 6; 15%), stalk (n = 6; 15%), roots (n = 5; 12%), inflorescence (n = 3; 7%), and branches (n = 1; 2.5%) (Figure 3). Approximately 56% (n = 23) of the studies used *Piper* structures to extract crude extracts and 44% (n = 18) used *Piper* structures to extract essential oils.

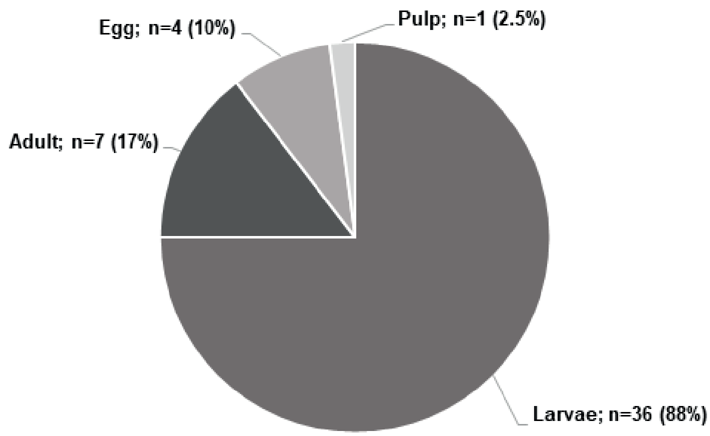
Figure 3. Plant structures of *Piper* used in studies (2002–2022) to control *Aedes aegypti* and *A. albopictus*, which were selected from Scopus, PubMed, and Google Scholar databases. The values in graph can exceed 100% because the same study may have included more than one plant structure.



Source: Research data

In the articles research, *A. aegypti* was the most commonly used biological model (n = 40/41; 97.5%), followed by *A. albopictus* (n = 4/41; 10%). Larvae were the mosquito phase most frequently used in the bioassays (n = 36/41; 88%), followed by adults (n = 7/41; 17%), eggs (n = 4/41; 10%), and pupae (n = 1/41; 2.5%) (Figure 4).

Figure 4. Ontogenic form most often used in studies (2002–2022) to control *A. aegypti* and *A. albopictus*, which were selected from Scopus, PubMed, and Google Scholar databases. The graph may exceed 100% due to the same work using more than one ontogenic form of mosquito in the bioassays.



Source: Research data

The LC_{50} values were reported in 33 articles (80.5%). For larvae, studies (n = 31/36; 86%) reported values of 0.17–1174.34µg/mL. These data were representative of the extracts of *P. hispidum* leaves and *P. ribesioides* branches. For adults, LC_{50} values were presented in only three of the seven studies (approximately 43%), with a variation of 0.64–139 µg/mL. These data are representative of the essential oils from *P. betle* leaves and various plant structures of *P. capitarianum*. The LC_{50} for eggs was mentioned in only one of the four studies (25%) that used essential oils extracted from the leaves of *P. alatipetiolatum*. The LC_{50} values obtained in this study was 9.33–65.06 µg/mL. Studies that used bioassays with pupae did not mention or determine LC_{50} (Table 2).

Complementally, we also evaluated the chemical compounds identified in the selected studies. Chemical analyses were performed in 28 articles (68%). Thus, it was possible to observe a variety of isolated compounds. Of these compounds, the most frequently mentioned were: -selinene, -pinene, pelitorin, E-caryophyllene, linalool, and germacrene D (Table 2).

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Table 2. A detailed description of the isolated chemical compounds and LC_{50} values of extracts and essential oils of *Piper* structures used in insecticidal bioassays against *Aedes aegypti* and *A. albopictus* mosquitoes in studies published between 2002 and 2022.

Species of *Piper*	**LC50**	**Chemical compound isolated**	**Authors**
P. aduncum	0.20 mg/cm^2	NR	Hidayatulfathi *et al*. (2004)
P. guineense	1.7µg/mL	NR	Oke *et al*. (2007)
P. nigrum	0.98µg/mL	Piperine and piperolein-A	Simas *et al*. (2007)
P. gaudichaudianum *P. humaytanum* *P. permucronatum* *P. hostmannianum*	121µg/mL 156µg/mL 36µg/mL 54µg/mL	Viridiflorol, aromadendrene, b-selinene, caryophyllene oxide, dillapiole, myristicin, and asaricin	Morais *et al*. (2007)
P. marginatum	19.9 – 23.8µg/mL	Monoterpenes, (E)-asarone, and patchouli alcohol	Autran *et al*. (2009)
P. aduncum *P. marginalum* *P. nigrum*	*Piper aduncum*: 30.2µg/mL *Piper marginatum*: 8.3 µg/mL *Piper nigrum:* 75.8µg/mL	-pinene, E-caryophyllene, santolitriene, limonene, caryophyllene oxide, sabinene, iso-elemycin, apiol, and -guaiene	Costa *et al*. (2010)
P. nigrum	127µg/mL	NR	Briones *et al*. (2012)
P. nigrum	1.84µg/mL	Piperine	Grzybowski *et al*. (2013)
P. ovatum	2.9-92µg/mL	Piperlongumine and piperine	Kanis *et al*. (2013)
P. nigrum	35µg/mL	Pipilyasine, Pipzubedine, Pipyaqubine, Pelitorine, Pipericin, and Piperine	Gulzar *et al*. (2013)
P. aduncum	134.1 – 289.9 µg/mL	Monoterpenes and sesquiterpenes	Oliveira *et al*. (2013)
P. klotzschianum	10 – 15.43µg/mL	1-Butyl-3,4-methylenedioxybenzene, 2,4,5-trimethoxy-1--propenylbenzene, limonene, and -phellandrene	Nascimento *et al*. (2013)
P. nigrum	7.12µg/mL	Oleic acid	Santiago *et al*. (2015)

Species of *Piper*	LC50	Chemical compound isolated	Authors
P. arboreum *P. marginatum* *P. aduncum*	*Piper arboreum*: 55µg/mL *Piper marginatum*: 34µg/mL *Piper aduncum*: 46µg/mL	Germacrene D, bicyclo-germacrene, (E)-methyl--isoeugenol, (E)-anethole, (Z)-methyl-isoeugen, (E)--isocroweacin, apiole, and elemycin	Santana *et al.* (2015)
P. nigrum	34.97µg/mL	Thymol and ç-elemen	Lija-Escaline *et al.* (2015)
P. augustum *P. corrugatum* *P. curtispicum* *P. darienense* *P. grande* *P. hispidum* *P. jacquemontianum* *P. longispicum* *P. multiplinervium* *P. reticulatum* *P. trigonum*	NR	Cembratrienol, -pinene, -pinene, trans--farnesene, p-cymene, dilapiole, linalool, -phellandrene, limonene, -caryophyllene, linalool, -phellandrene, p-cymene, -selinene, - element, -selinene, and germacrene D	Santana *et al.* (2016)
P. nigrum	3.1-5.3µg/mL	Piperine	Custódio *et al.* (2016)
P. betle	0.64-0.72µg/mL	NR	Vasantha-Sriniva-san *et al.* (2017)
P. hispidum *P. aduncum*	*P. hispidum*: 0.169µg/mL *P. aduncum:* 0.342µg/mL	NR	Porto *et al.* (2017)
P. betle	0.63µg/mL	Eudesm-7(11)-en-4-ol, 2H-cyclopentacyclooctene, 4,5,6,7,8,9-hexahydro--1,2,2,3-tetramethyl and 5-hydroxy-8, 8-dimethyl l-3,3a,4,5,6,7,8,8b oc-tahydroindene	Vasantha-Sriniva-san *et al.* (2018)
P. ovatum	2.6µg/mL	NR	Kanis *et al.* (2018)
P. ribesioides	411.89 – 1174.34µg/mL	Piperine	Kumrungsee *et al.* (2018)

Species of *Piper*	LC50	Chemical compound isolated	Authors
P. betle	59.8-183µg/mL	NR	Martianasari; Hamid (2019)
P. aduncum	25.7µg/mL	Dilapiol	Scalvenzi *et al.* (2019)
P. crocatum	NR	Aromatic compounds and terpenes	Setiawan *et al.* (2019)
P. klotzschianum *P. hispidum* *P. arboreum*	*P. klotzschianum:* 122.4 - 223.1µg/mL *P. hispidum*: 141.9µg/mL *P. arboreum*: 187.9µg/mL	Germacrene D, bicyclogermacrene, (E)-caryophyllene, and -3-carene	Lima *et al.* (2019)
P. alatipetiolatum	Larvicidal assay: 6.37 – 33.741µg/mL Ovicidal assay: 9.33 – 65.06µg/mL	Sesquiterpenes	Oliveira *et al.* (2020)
P. corcovadensis	4.86µg/mL	Piperovatin	Fernandez *et al.* (2020)
P. dilatatum *P. hostmannianum*	*P. dilatatum*: 97.56µg/mL *P. hostmannianum*: 96.13µg/mL	NR	Albuquerque *et al.* (2020)
P. longum	50.81 – 395.51µg/mL	Eugenol, n-Hexadecanoic acid, Phytol, Oleic Acid, 4-Chromanol, 2,4-Di tert butylphenol, Tetradecanoic acid, Phenol, 4-(2-propenyl), cis-Vaccenic acid, Butanoic acid, 9,12-Octadecadienoyl chloride, (Z,Z)	Dey *et al.* (2020)
P. capitarianum	*Larvae/A. aegypti*: 82.43 – 139.5µg/mL Larvae/A. albopictus: 63.5 – 133.83µg/mL Adults/A. aegypti: 126.25 – 140.36µg/mL Adults/A. albopictus: 124.5 – 139µg/mL	Rans-caryophyllene, -humulene, -myrcene, -selinene and linalool	França *et al.* (2021)

Species of *Piper*	LC50	Chemical compound isolated	Authors
P. longum	0.22 – 0.47µg/mL	Isopropyl myristate, N-hexadecanoic acid, Dodecane, Heneicosane, and Docosane	Priya *et al*. (2021)
P. sarmentosum	39.04 – 156.10µg/mL	Phenylpropanoids (Z-isoelemicin and asarone)	Othman *et al*. (2021)
P. umbellatum	NR	Tannins, flavonoids, and phenolic compounds	Oliveira *et al*. (2021)
P. kadsura	NR	Pellitorin, Chingchengenamide A, and Piperenone	Seo *et al*. (2021)
P. purusanum	*A. aegypti*: 53.41 µg/mL. *A. albopictus*: 42.62µg/mL.	-caryophyllene, -humulene, and germacrene D	Oliveira *et al*. (2022)

NR = analysis not performed. Studies that did not calculate LC50 and did not investigate the chemical compounds present in natural products derived from *Piper* were not included in this table.

4 DISCUSSION

Plants of the *Piper* genus have promising biological activities against *Aedes* spp. and in this review, this knowledge was updated to confirm the potential of *Piper* to produce natural compounds to control these vectors.

Our data demonstrated that the three *Piper* species most commonly used in experiments against *A. aegypti* and *A. albopictus* were *P. aduncum*, *P. nigrum*, and *P. marginatum.* Previous studies (TORRES-PELAYO *et al*., 2016; DURANT-ARCHIBOLD *et al*., 2018) have indicated that *P. aduncum* is used in several traditional formulations as an astringent, digestive stimulant, diuretic, antimalarial, sedative, and remedy for haemorrhoids, gonorrhoea, diarrhoea, and toothache. Furthermore, Misni *et al*. (2011) reported that the essential oil of *P. aduncum* has the potential to be used as a spray formulation against adults of *A. aegypti* and *A. albopictus*.

Piper nigrum (black pepper) is a widely used spice is known for its chemical constituent called piperine (MEGHWAL; GOSWAMI, 2013). Based on studies in cell cultures, vertebrate experimental models, and humans, piperine has been found to have immunomodulatory, antioxidant, anti-asthmatic, anti-cancer, anti-inflammatory, anti-ulcer, and anti-amoebic properties (MEGHWAL; GOSWAMI, 2013). Furthermore, Lija-Escaline *et al*. (2015) demonstrated that the botanical extract of *P. nigrum* showed remarkable larvicidal activity against *A. aegypti,* severely affecting its intestinal cells.

In addition, *P. marginatum* is popularly known as "pimenta-do-mato", and it has been demonstrated that the essential oil derived by this plant has strong larvicidal activity against *A. aegypti* (AUTRAN *et al*.,

2009) and fungicidal activity against *Fusarium oxysporum* (SANTOS *et al*., 2011). Therefore, these data may explain the potential of these three species in experimental studies on *A. aegypti* and *A. albopictus*.

The leaves were most commonly used to obtain extracts and essential oils. Indeed, the leaf is the easiest element of the plant to collect, and its removal induces less damage than other structures (e.g., roots and stems). In most plant species, the leaves are available throughout the year. Although crude extracts are simple to produce, in our study, we did not observe substantial differences in their use in bioassays compared to essential oils. Both natural products are widely commercialised in traditional medicine because of their antioxidant and antimicrobial properties (TONGNUANCHAN; BENJAKUL, 2014). In addition, the use of products derived from plants for insecticide purposes is a tradition more than 3000 years old, which still persists today (PAVELA, 2016).

In the bioassays, *A. aegypti* larvae were the most commonly-used experimental models. This species is considered one of the most important vectors of arboviruses worldwide (NÄSLUND *et al*., 2021) and has received attention from researchers. Furthermore, the larval stage of *A. aegypti* is the most susceptible to adverse effects compared to the pupal and egg stages (PRICE; MILLS, 1988) which explains the large number of studies that have conducted larvicidal assays.

Lethal concentration (LC) values are frequently determined to measure the biological activity of natural products in experimental bioassays. The crude extract from *P. hispidum* leaves and essential oil from *P. betle* leaves had the lowest LC_{50} values in experimental assays against larvae and adults of *A. aegypti*, respectively. These natural products are among the most promising of those observed in the current review. However, it is necessary to investigate the LC_{50} values of these two products in nontarget organisms to confirm their environmental safety. These nontarget organisms generally have a reference physiological response that represents various trophic levels of the ecosystems (SILVA *et al*., 2015). Thus, in these bioassays, it is possible to estimate the extent of the environmental and health impacts of synthetic and natural compounds (LINDE-ARIAS *et al*., 2008; SILVA *et al*., 2015). However, toxicity studies on products derived from plants are still poorly performed, because persists the general idea that plants and their components are generally natural and safe (FERRAZ *et al*., 2022).

In this review, -selinene, -pinene, pelitorin, E-caryophyllene, linalool, germacrene D were frequently found. According to Pereira *et al*. (2014), linalool can enhance the larvicidal effect of the essential oil of *Pimenta dioica* leaves against *A. aegypti*, and Miranda *et al*. (2002) demonstrated that pelitorin had an insecticidal effect against *Diatraea saccharalis* (Lepidoptera: Crambidae). These chemical compounds may explain the biological activity of natural products derived from *Piper* plants against *Aedes* spp. and deserve more attention in future studies.

Although we have found a variety of compounds derived from *Piper* that are biologically active against *A. aegypti* and *A. albopictus*, few commercially available products are still derived from them. Part of this problem is related to the low stability of these products in the environment, which promotes rapid degradation and unsatisfactory biological effects (TUREK; STINTZING, 2013). In addition, many plants are difficult to produce on a large scale, and there is insufficient government support to stimulate the production (PAVELA, 2016). Despite these bottlenecks, studies on the biological effects of products derived from *Piper* plants must continue, to promote the discovery of new highly effective molecules against *Aedes* with reduced environmental toxicity.

5 CONCLUSION

Our review demonstrates that the *Piper* genus has the potential to control mosquitoes of the species, *A. aegypti* and *A. albopictus*, which are considered the main vectors of arboviruses worldwide. The most commonly used species were *P. aduncum, P. nigrum*, and *P. marginatum*. The leaves were most commonly used for the production of extracts and essential oils to perform larvicidal assays against *A. aegypti*. The biological action of *Piper* against *Aedes* may be connected to the chemical compounds present in the extracts and essential oils, such as -selinene, -pinene, pelitorin, E-caryophyllene, linalool, and germacrene D. This review describes the advances over the years in the study of natural products derived from *Piper* species to fight *Aedes* mosquitoes and may inform new prophylaxis for these vectors.

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1 Biólogo. Instituto Federal do Maranhão – IFMA, São Raimundo das Mangabeiras, MA, Brasil. ORCID 0000-0003-0383-2067. Email martinslimamarcos@gmail.com

2 Bióloga. Programa de Pós-Graduação em Agricultura e Ambiente. Universidade Estadual do Maranhão – UEMA, São Luís, MA, Brasil. ORCID 0000-0002-4779-9361. Email: tamiresmouralima2016@gmail.com

3 Biólogo. Programa de Pós-Graduação em Ecologia e Conservação da Biodiversidade. Universidade Estadual do Maranhão – UEMA, São Luís, MA, Brasil. ORCID 0000-0002-4506-242X. Email: kaiobiolog202@gmail.com

4 Biólogo. Programa de Pós-Graduação em Biodiversidade e Conservação. Universidade Federal do Piauí – UFPI, Floriano, PI, Brasil. ORCID 0000-0003-3486-9639. Email: rafael.loreto12@gmail.com

5 Biólogo, Doutor em Parasitologia. Programa de Pós-Graduação em Ecologia e Conservação da Biodiversidade, Curso de Ciências Biológicas, Departamento de Biologia, Universidade Estadual do Maranhão, São Luís, MA, Brasil. ORCID 0000-0003-0920-4977. Email: gustavorodrigues_98@hotmail.com

6 Biólogo, Doutor em Parasitologia. Professor do Instituto Federal do Maranhão – IFMA, campus São Raimundo das Mangabeiras, MA, Brasil. ORCID 0000-0003-3763-2776. Email: mirandagsbio@gmail.com

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