Plant Natural Products for the Control of *Aedes aegypti*: The Main Vector of Important Arboviruses

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Abstract: The mosquito species *Aedes aegypti* is one of the main vectors of arboviruses, including dengue, Zika and chikungunya. Considering the deficiency or absence of vaccines to prevent these diseases, vector control remains an important strategy. The use of plant natural product-based insecticides constitutes an alternative to chemical insecticides as they are degraded more easily and are less harmful to the environment, not to mention their lower toxicity to non-target insects. This review details plant species and their secondary metabolites that have demonstrated insecticidal properties (ovicidal, larvicidal, pupicidal, adulticidal, repellent and ovipositional effects) against the mosquito, together with their mechanisms of action. In particular, essential oils and some of their chemical constituents such as terpenoids and phenylpropanoids offer distinct advantages. Thiophenes, amides and alkaloids also possess high larvicidal and adulticidal activities, adding to the wealth of plant natural products with potential in vector control applications.

Keywords: *Aedes aegypti*; dengue; natural products; botanical species; essential oils; terpenes; phenylpropanoids; thiophenes; alkaloids; mechanisms of action

1. Introduction

The mosquito *Aedes aegypti* (Diptera: Culicidae) originated in Egypt and it is widely distributed in tropical and subtropical regions, including North America and Europe [1,2]. *Ae. aegypti* presents complete metamorphosis from immature egg, larva and pupa stages to the adult mosquito itself (Figure 1). The life cycle varies according to environmental temperature, food availability and quantity of larvae in the same breeding site. Under favorable conditions, after egg hatching, the mosquito transforms into the adult stage within 10 days, even though the eggs can be viable up to 450 days in the absence of water [3].

The female mosquito requires hematophagy for egg maturation. Viral transmission to humans occurs during this process if the mosquito is infected. The lifetime of a female mosquito is approximately 45 days [1]. *Ae. aegypti* population control is considered the principal measure to combat arboviral diseases as this species is the primary vector of dengue, Zika, chikungunya and urban yellow fever [4,5].

In 2012, dengue was considered the mosquito-borne disease of major importance in the world [5]. According to the World Health Organization, 390 million people are infected annually with the dengue virus, 96 million of which have clinical manifestations [6]. There are various symptoms, the first is usually high fever (39–40 °C) with headache, prostration, arthralgia, anorexia, asthenia, nausea, among others. Some clinical aspects often depend on patient age. There is no specific treatment for dengue and the more complicated cases of the disease can cause hemorrhage, shock and even death [7].
Aedes aegypti is considered the main Zika virus vector (Figure 1), but infection can also occur by sexual transmission or blood transfusion [8]. Symptoms are non-specific and self-limited, being easily confused with other arboviral diseases. Some important complications exist, such as microcephaly in fetuses and Guillain-Barré syndrome. The virus has been reported in countries in Americas, Europe, Asia and the Pacific region [8]. Like dengue and Zika, chikungunya has no specific treatment. The disease emerged in the Americas in 2013, with about 1.7 million cases identified and 252 deaths reported by August 2015 [9].

In 2013, dengue generated a global cost of US $8.9 billion, with around 58.4 million symptomatic cases (13.5 million fatalities) in the 141 countries and territories. The per capita costs of dengue were $70.1 for hospital treatment, $51.1 for outpatient treatment and $12.9 for cases that did not reach the health system. According to this study, Brazil had an incidence of 751 to 1,000 cases per 100,000 people. The expenses were proportional to the incidence and ranged from $2.5 to $5 for each treated case [10].

A more recent study showed that in 2016 the Brazilian government spent around R $805 million (ca. 160 million US$) to treat diseases caused by the Aedes aegypti mosquito, including direct medical expenses and indirect costs. In addition, about R $1.5 billion were destined to combat the vector, totaling R $2.3 billion, that was 2% of the health budget for that year. More than 2 million cases of Aedes aegypti related diseases were verified. These numbers were underestimated as they did not include complications such as microcephaly and Guillain-Barré syndrome [11].

A study estimated that about 60% of the world population will be at risk of dengue in 2080, which represents over 6.1 (4.7–6.9) billion people [12]. Considering that vector control is the main tool for controlling these expensive arboviruses, investment in techniques to combat the Aedes aegypti mosquito is growing [3]. Investments are particularly focused on techniques with minimal negative impacts on non-target animals and the environment [4,13].

2. Mosquito Control

There are several techniques already used to combat mosquitoes, which act both in the immature phases (egg, larva and pupa) and in the adult [13]. Highly toxic synthetic insecticides such as organophosphates, pyrethroids and carbamates have been historically used to combat the mosquito, acting mainly on insect larvae [4]. More recently, insecticides with less toxicity which are less persistent in the environment have been developed, including neonicotinoids and oxadiazines [14]. However, these products are still widely used and harmful to living organisms and the environment, and the use of foogers and aerial applications of sintetic insecticides against adults, such as pyrethroids

Figure 1. Aedes aegypti life cycle and the main arboviruses transmitted by the female mosquito.
products, contributes to insect resistance problems [4]. Therefore, efforts must be made to ensure newly developed alternative insecticides are more eco-friendly.

Biological tools that control the adult stage are based on behavior, such as the Sterile Insect Technique (SIT), Incompatible Insect Technique (IIT) and Release of Insects carrying a Dominant Lethal gene (RIDL), which involve insect sterilization by chemical irradiation, natural bacteria which are pathogenic for mosquito (highly specific strains of Wolbachia) and genetic modifications to make sterile male mosquitoes, respectively [15,16]. The other technique applied against the adult stage is the use of entomopathogenic fungi, specifically in the orders Entomophthorales, Hypocreales and Pezizales due to their specificity, ability to manipulate and infectiveness to the host [17].

*Ae. aegypti* control using specific strains of Wolbachia bacteria is currently practiced in different locations around the world through the World Mosquito Program. This program involves the application of the bacteria to laboratory mosquitoes that are released into the local *Ae. aegypti* population during reproduction. The presence of bacteria in mosquitoes decreases the possibility of arbovirus transmission to people [18].

Biological control tools that act against the immature stages include the application of *Bacillus thuringiensis* in larvae habitats; products that prevent oviposition and/or inhibit growth and reproduction, including pheromones. There are also natural predators such as fish (especially of the genus Gambusia and Poecilia, family Poeciliidae) [19,20], copepods (including several species of the genus Mesocyclops) [21,22] and the “elephant mosquito” (genus Toxorhynchites) [23,24].

Finally, plant-based insecticides (ovicides, larvicides and pupicides) [25,26] deserve a special mention due to the vast biodiversity of species found in the world, estimated to be approximately 400,000 terrestrial species [27]. Botanical insecticides can be plant extracts, essential oils and/or secondary metabolites [4,14].

3. Plant Natural Products to Control Mosquitoes

The search for plant natural products to control *Ae. aegypti* dates back a number of years, with research published since the 1980s [28,29]. However, chemical insecticides are most commonly used, despite their enormous toxicity to non-target organisms, such as: (i) poisoning and death; (ii) cancer, by non-genotoxic mechanisms (immunosuppressants, cytotoxic) or by triggering the carcinogenic process in different ways; (iii) harmful effects on the nervous, renal, respiratory and reproductive systems and (iv) induction of oxidative stress [30].

In addition to toxicity, another concern is the increasing resistance of the mosquito vector to chemical insecticides. One example is the knockdown resistance (*kdr*) mutation, in which resistance to pyrethroid insecticides occurs, whereby the target site is the sodium channel of the *Ae. aegypti* nervous system [31,32]. In Brazil, of the five insecticides approved by the Public Health Ministry and recommended by the WHO for adult mosquito control, four belong to the pyrethroid class together with one organophosphate (malathion). However, in 2011 a technical note was issued suspending the use of pyrethroids in Brazil to control *Ae. aegypti* [33].

The level of resistance is dependent on the insecticide concentration, frequency and duration of application [34]. The resistance mechanisms of mosquitoes may be associated with changes in the insect cuticle resulting in less insecticide absorption [35], changes in insect metabolism involving biotransformation enzymes [36,37] and modifications of the insecticide target site, usually by genetic mutations [38,39].

The main esterases involved in the resistance process are carboxylesterases and cholinesterases. Carboxylesterases are usually resistant to organophosphates, with this resistance relating to both a quantitative mechanism (overproduction of enzyme) and qualitative mechanism (mutations that cause alterations in enzymatic properties) [40]. In the case of cholinesterases, the resistance is mainly caused by gene mutation. The main insecticides resistant to the acetylcholinesterase target site are organophosphates and carbamates [41].
Another problem associated with chemical insecticides is the damage caused to the environment and living organisms by their degradation products, which may prove more toxic than the original product itself. Examples include the degradation products of temephos, whose effects have already been documented in aquatic environments [42], and malathion, together with its metabolites, in non-target organisms such as *Daphnia magna* (Cladocera: Daphniidae) [43].

Insecticides derived from plant natural products therefore offer a promising source of safer new products for mosquito control due to minimal residues from its natural degradation in both the field and in water, minimizing ecosystem disruption [44,45]. There is considerable research on insecticides of natural origin, especially those of microbial and plant origin, due to their innumerable secondary metabolites produced especially as a defense mechanism against natural predators [46]. It is estimated that there are more than 100,000 plant metabolites, with hundreds or more exhibiting some activity against insects [47].

Botanical insecticides are advantageous as they are generally environmentally safe, non-toxic to non-target organisms including homeothermic animals and their residues biodegradable [25,26,30]. The synergic mixture of the active compounds in extracts induce several mechanisms of action and result in less pest resistance [30,48].

The present review focuses on the more recent studies of botanical extracts and active compounds in applications against *Ae. aegypti*, from immature to adult stages, in addition to their main proposed mechanisms of action. The crude extracts are obtained using different extraction methods with organic solvents or water. Essential oils are obtained by steam distillation or hydrodistillation. The classes of active compounds include terpenes, alkaloids and amides, steroids, flavonoids, furanochromones, phenylpropanoids and phenol derivatives, lignans and neolignans, naphthoquinones, fatty acids and their derivatives. The type of insecticide activity (ovicide, larvicide, pupicide, adulticide) is reported as mortality and lethal concentration values (LC$_{50}$, LC$_{90}$ and/or LC$_{99}$), together with egg hatchability. The other activities tested are mosquito repellency, oviposition deterrence, growth regulation and the antifeedant effect.

4. Essential Oils

Essential oils deserve special attention as they have yields of 0.5 to 2.0% in the extraction process, contain a high concentration of secondary metabolites and generally present potent activity due to the synergistic effect of the constituents. An important advantage is, with few exceptions, their relatively low, or no, toxicity to mammals (Figure 2). Some pure compounds constituents of essential oils are moderately toxic to mammals (LD$_{50}$ 800–3000 mg/kg in rodents) while formulated products usually are low or non-toxic to mammals, birds and fish (LD$_{50}$ above 5000 mg/kg for rodents) [47,49].

Figure 2. Essential oils to combat the *Ae. aegypti* mosquito: an ecologically safe alternative.
These essential oils are mainly obtained from aromatic plants, of which there are more than 3000 species. Approximately 10% of these are already produced in large quantities for other uses, such as flavorings and fragrances, and are therefore readily available at reasonable prices [30]. Essential oils are composed of volatile compounds, which give an important advantage of non-persistence in the environment [49,50].

It is important to note that the same volatility may be a disadvantage in terms of instability. However, this property can be overcome using pharmaceutical technology such as micro and nanoencapsulation [51,52]. Formulation development is therefore critical for essential oils to be used effectively and safely as pesticides. A number of studies have demonstrated that a suitable vehicle prolongs the insecticidal effect [51,53,54].

Of the plant families affording essential oils, those most tested against *Ae. aegypti* larvae were Myrtaceae, in particular *Eucalyptus* species, followed by Fabaceae, Asteraceae, Apiaceae and Lamiaceae. Asteraceae was the most important for the adulticide, repellent and oviposition effects.

Regarding larvicidal activity there is currently no value specified by the WHO to discriminate whether a compound or extract is active against insects. However, researchers usually consider that an LC$_{50}$ < 50 µg/mL is very active; an LC$_{50}$ 50–100 µg/mL is active, and an LC$_{50}$ > 100 µg/mL is weak/inactive [55–57].

![Figure 3](image-url)

**Figure 3.** Secondary metabolites identified in essential oils with insecticidal activity against the *Ae. aegypti*. (A) Alkanes (B) Terpenes and (C) Phenylpropanoids.
Considering this classification, this review highlights 11 species with 12 very active essential oils, 11 species with 14 active essential oils and 6 species with weak/no activity for 7 essential oils. Eight species do not have reported LC$_{50}$ values and are not considered in this classification. However, these values can change significantly after formulation, as discussed in Section 8 “Limitations and/or Expectations of Plant Natural Product Insecticide Applications”.

Some studies made the identification of secondary metabolites in essential oils evaluated for insecticidal activities described above and its chemical structures are illustrated in Figure 3.

Tables 1 and 2 summarise the publications selected for this review and discussion of the essential oils active against the Ae. aegypti mosquito. Table 1 describes larvicidal activities, while Table 2 details the adulticidal, repellent and oviposition activities.

The essential oil from Acacia nilotica (L.) Delile (Fabaceae) seeds had the highest insecticidal activity (LC$_{50}$ 3.17 µg/mL). The major compounds were hexadecane (I) and heptacosane (2) [58]. This species has been investigated for several medicinal uses including spasmogenic and antiplasmodial activities of seed extracts [59].

Another species is Myristica fragrans Houtt. (Myristicaceae), which is popularly known as nutmeg and is used as a flavoring. Essential oil from its seeds demonstrated high toxicity against Ae. aegypti, in both the L3 larval phase (LC$_{50}$ 28.2 µg/mL) and the adult phase (LC$_{50}$ 18.5 µg/mg female). The major compounds identified were sabinene (3, 52%), α-pinene (no stereochemistry defined, 4) (13%) and terpen-4-ol (5) (11%). Regarding neurotoxic effects, this essential oil is non-toxic to humans as its IC$_{50}$ values for human acetylcholinesterase and human butyrylcholinesterase are higher than 4000 µg/mL [54]. Nutmeg flower essential oil presented higher larvicidal activity (LC$_{50}$ 47.42 µg/mL) than the ethanolic extract (LC$_{50}$ 75.45 µg/mL). This result suggests that the constituents of the essential oil either exhibit higher larvicidal activity, or that the synergy between them favors the toxicity to the mosquito [60].

Eucalyptus species (Myrtaceae) leaf essential oils showed LC$_{50}$ values in the range of 31.0–95.5 µg/mL for the larvae stage and 100% repellency for 1.5 h. Eucalyptus camaldulensis Dehn. had the highest larvicidal activity while Eucalyptus saligna Sm. displayed higher repellency than Eucalyptus nitens (H. Deane & Maiden) Maiden [61–63].

Cinnamomum osmophloeum Kanhe. (Lauraceae) is commonly named pseudocinnamomum and the essential oil from leaves of different places demonstrating larvicidal activities of LC$_{50}$ 36 to 177 µg/mL [64]. Similar variation was observed in the larvicidal activity of different guava crops. The LC$_{50}$ values of Psidium guajava L. (Myrtaceae) leaf essential oil ranged from 39.48 to 64.25 µg/mL [65].

Other edible plant essential oils that showed strong larvicidal activity were parsley [Petroselinum crispum (Mill.) A.W. Hill (Aipiacae)], fennel [Foeniculum vulgare Mill. (Aipiacae)], star anise [Illicium verum Hook. f. (Illiciaceae)], Piper sarmentosum Roxb. ex Hunt. (Piperaceae) and sucupira [Pterodon emarginatus Vogel (Fabaceae)] [54,60,66].

For parsley, the toxicity was evaluated for pyrethroid-susceptible and pyrethroid-resistant mosquitoes (LC$_{50}$ 40 µg/mL) and the major metabolite was thymol (6). Similar toxicity was observed for fennel (LC$_{50}$ 44.84 µg/mL), for star anise (LC$_{50}$ 39.8 µg/mL) and for Piper sarmentosum (LC$_{50}$ 49.19 µg/mL) [54,60]. The major constituent of star anise essential oil was trans-anethole (7, 90%) [54]. Furthermore, parsley and star anise essential oils demonstrated adulticidal activity with LC$_{50}$ 6.01 µg/mg female for pyrethroid-susceptible, LC$_{50}$ 6.15 µg/mg female for pyrethroid-resistant (Petroselinum crispum) and LC$_{50}$ 10.3 µg/mg female for Illicium verum [54,60].

A sucupira (Pterodon emarginatus) fruit essential oil incorporated into a nanoemulsion to improve water solubility and increase product stability presented an LC$_{50}$ 34.75 µg/mL. The metabolites were identified as β-caryophyllene (8), geranylgeraniol (9) and 6α,7β-dihydroxyvouacapan-17-β-oi acid (10). The toxicity for non-target organisms was tested in adult female Swiss albino mice [Mus musculus (Rodentia: Muridae)] with no behavioral effects, macroscopical changes or deaths reported [66].
| Plant Species | Family       | Country     | Part Used | Larval Stage | Mortality | Time of Analysis (h) Reference |
|---------------|--------------|-------------|-----------|--------------|-----------|------------------------------|
| Acacia nilotica (L.) Delile | Fabaceae     | India       | Seeds     | L4           | % Death  | Concentration (ppm) | LC50 (ppm) | LC90 (ppm) | | | |
|              |              |             |           |              | 3.17      | 11.73         | 24       | [58]        |
| Alpinia purpurata (Vieill.) K. Schum. | Zingiberaceae | Brazil      | Red flowers | L4           | ND        | ND             | 80.70    | ND         | 24       | [67]        |
| Baccharis reticularia DC. | Asteraceae   | Brazil      | Leaves    | L4           | ND        | ND             | 71.50    | ND         | 24       | [68]        |
| Bauhinia pulchella Benth. | Fabaceae     | Brazil      | Leaves    | L3           | ND        | ND             | 105.90   | ND         | 24       | [69]        |
| Bauhinia unguulata L. | Fabaceae     | Brazil      | Leaves    | L3           | ND        | ND             | 75.10    | ND         | 24       | [69]        |
| Cinnamomum osmophloeum Kaneh. | Lauraceae    | Taiwan      | Leaves    | L4           | ND        | ND             | 36.0 to 177.0 | 79.0 to 296.0 | 24       | [64]        |
| Croton rhamnifoliosus Pax & K. Hoffm. | Euphorbiaceae | Brazil      | Leaves    | L4           | ND        | ND             | 122.30   | ND         | 24       | [70]        |
| Curcuma longa L. | Zingiberaceae | Thailand    | Rhizome   | L4 (p-s)     | ND        | ND             | 65.51    | ND         | 24       | [60]        |
| Eucalyptus camaldulensis Dehnh. | Myrtaceae    | Taiwan      | Leaves    | L4           | ND        | ND             | 31.0     | ND         | 24       | [61]        |
| Eucalyptus nitens (H. Deane & Maiden) Maiden | Myrtaceae    | Argentina   | Leaves    | L3/L4        | ND        | ND             | 52.83    | ND         | 24       | [62]        |
| Eucalyptus urophylla S.T. Blake | Myrtaceae    | Taiwan      | Leaves    | L4           | ND        | ND             | 95.50    | 166.30     | 24       | [61]        |
| Feronia ilicifolia Boiss. & Buhse | Apiceae      | Corea       | Resin     | L3           | 90        | 100.0          | ND       | ND         | 48       | [45]        |
| Foeniculum vulgare Mill. | Apiceae      | Thailand    | Fruit     | L4 (p-s)     | ND        | ND             | 44.84    | 57.05      | 24       | [60]        |
| Hyospus officinalis L. | Lamiaceae    | Corea       | Flowers   | L3           | 95        | 100.0          | ND       | ND         | 48       | [45]        |
| Illicium verum Hook. f. | Illiciaceae  | Brazil      | Fruit     | L3           | 93.80     | 53.0           | ND       | ND         | 24       | [54]        |
| Larix europea Lam. & A. DC. | Pinaceae     | Corea       | Resin     | L3           | 87        | 100.0          | ND       | ND         | 48       | [45]        |
| Limonoplia aromatica (Lam.) Merr. | Scrophulariaceae | Thailand | Whole plant | L4 (p-s) | ND | ND | 47.94 | 65.14 | 24 | [60] |
| Mentha spicata L. | Lamiaceae    | Corea       | Seeds     | L3           | 28.20     | 41.70          | ND       | ND         | 24       | [54]        |
| Myroxylon pereirae (Royle) Klotzsch | Myristicaceae | Thailand    | Flowers   | L4 (p-s)     | ND        | ND             | 47.42    | 69.28      | 24       | [60]        |
| Myroxylon graviolens L’Her. ex Aiton | Geraniaceae  | Corea       | Resin     | L3           | 97.5      | 100.0          | ND       | ND         | 48       | [45]        |
| Pimenta dioica (L.) Merr. | Myrtaceae    | Corea       | Seeds     | L3           | 82        | 100.0          | ND       | ND         | 48       | [45]        |
| Pinus sylvestris L. | Pinaceae     | Nigeria     | Needles   | L4           | ND        | ND             | 104.40   | 137.30     | 24       | [54]        |
| Piper aduncum L. | Piperaceae   | Brazil      | Leaves    | L3/L4        | ND        | ND             | 289.90   | 654.90     | 24       | [74]        |
Table 1. Cont.

| Plant Species                      | Family     | Country        | Part Used            | Larval Stage | Mortality | Concentration (ppm) | LC<sub>50</sub> (ppm) | LC<sub>90</sub> (ppm) | Time of Analysis (h) | Reference |
|-----------------------------------|------------|----------------|----------------------|--------------|-----------|---------------------|------------------------|------------------------|----------------------|-----------|
| *Piper sarmentosum* Roxb. ex Hunt.| Piperaceae | Thailand       | Stem and leaves      | L₄ (p-s)     | ND        | ND                  | 49.19                  | 75.10                  | 24                   | [60]      |
| *Pogostemon patchouli* Pellet.    | Labiatae  | Corea          | Whole plant          | L₃           | 97        | 100.0               | ND                     | ND                     | 48                   | [45]      |
| *Porophyllum ruderale* (Jacq.) Cass.| Asteraceae | Brazil         | Flowers and leaves   | L₃           | ND        | ND                  | 60.90                  | 132.48                 | 24                   | [75]      |
| *Psidium guajava* L.              | Myrtaceae  | Brazil         | Leaves               | L₄           | ND        | ND                  | 39.48 to 64.25         | 57.34 to 86.0         | 24                   | [65]      |
| *Pterodon emarginatus* Vogel      | Fabaceae   | Brazil         | Fruit                | L₄           | ND        | ND                  | 34.75                  | ND                     | 48                   | [66]      |
| *Rosmarinus officinalis* L.       | Labiatae  | Brazil         | Leaves               | L₄           | 80        | 250.0               | ND                     | ND                     | 24                   | [76]      |
| *Sphaeranthus indicus* L.         | Asteraceae | India          | Leaves               | L₄           | 90        | 250.0               | ND                     | ND                     | 48                   | [77]      |
| *Syzygium aromaticum* (L.) Merr. & L.M. Perry | Myrtaceae | Nigeria        | Bud                  | L₄           | ND        | ND                  | 92.56                  | ND                     | 24                   | [73]      |
| *Tanacetum argenteum* (Lam.) Willd. subsp. argenteum (Lam.) | Asteraceae | Turkey         | Aerial parts         | L₁           | ND        | ND                  | 93.30                  | 241.70                 | 24                   | [78]      |
| *Trachyspermum ammi* (L.) Sprague | Apiaceae   | Corea          | Seeds                | L₃           | 100       | 100.0               | ND                     | ND                     | 48                   | [45]      |

LC<sub>50</sub> lethal concentration required to kill 50% of the larval population, LC<sub>90</sub> lethal concentration required to kill 90% of the larval population, ND not described, p-s pyrethroid-susceptible.
Table 2. Adulticidal, repellent and oviposition activities of essential oils against the *Ae. aegypti* mosquito.

| Plant Species                        | Family       | Country      | Part Used | Activity          | Results                                           | Time of Analysis (h) | Reference |
|--------------------------------------|--------------|--------------|-----------|-------------------|--------------------------------------------------|----------------------|-----------|
| *Acantholippia seriphoides* (A. Gray) | Verbenaceae  | Argentina    | ND        | Repellent         | 100% of repellency at 50%                        | 1.2                  | [63]      |
| Moldenke                             |              |              |           |                   |                                                  |                      |           |
| *Aloysia citriodora* Palau           | Verbenaceae  | Argentina    | ND        | Repellent         | 100% of repellency at 12.5%                      | 1.5                  | [63]      |
| *Alpinia purpurata* (Vieill.) K. Schum. | Zingiberaceae | Brazil       | Red flowers | Oviposition       | Oviposition disruptive effect                    | ND                   | [67]      |
| *Baccharis spartioides* (Hook. & Arn.) Remy | Euphorbiaceae | Brazil       | Pink flowers | Oviposition       | Oviposition disruptive effect                    | ND                   | [67]      |
| *Croton rhamnifolius* Pax & K. Hoffm. | Euphorbiaceae| Argentina    | ND        | Repellent         | 100% of repellency at 12.5%                      | 1.5                  | [63]      |
| *Eucalyptus nitens* (H. Deane & Maiden) | Myrtaceae    | Argentina    | Leaves    | Repellent         | 100% of repellency at 50%                        | 1.5                  | [62]      |
| Maiden                               |              |              |           |                   |                                                  |                      |           |
| *Eucalyptus saligna* Sm.             | Myrtaceae    | Argentina    | ND        | Repellent         | 100% of repellency at 50%                        | 1.5                  | [63]      |
| *Illicium verum* Hook. f.            | Illiciaceae  | Brazil       | Fruit     | Adulticide        | LC₅₀ 10.30 µg/mg female                          | 24                   | [54]      |
| *Mentha longifolia* Griseb           | Lamiaeceae   | Argentina    | ND        | Repellent         | LC₅₀ 17.50 µg/mg female                          | 24                   | [54]      |
| *Myristica fragrans* Houtt.          | Myristicaceae| Brazil       | Seeds     | Adulticide        | LC₅₀ 18.50 µg/mg female                          | 1.0                  | [63]      |
| *Pluchea carolinensis* (Jack.) G.    | Asteraceae   | Martinica    | Leaves and flowers | Repellent | 100% of repellency at 1.0%                      | ND                   | [79]      |
| *Rosmarinus officinalis* L.          | Lamiaeceae   | Argentina    | ND        | Repellent         | 36.6% of repellency at 1.0%                      | ND                   | [79]      |
| *Sphaeranthus indicus* L.            | Asteraceae   | India        | Leaves    | Adulticide        | 30.6% of mortality at 0.1%                        | 3.5                  | [77]      |
| *Tagetes minuta* L.                  | Asteraceae   | Argentina    | ND        | Repellent         | 100% of repellency at 200 ppm                    | 24                   | [77]      |
| *Tagetes minuta* L.                  | Asteraceae   | Argentina    | ND        | Repellent         | 100% of repellency at 25%                        | 1.5                  | [63]      |

LC₅₀: lethal concentration required to kill 50% of the mosquito population, LC₉₀: lethal concentration required to kill 90% of the mosquito population, ND: not described, p-s: pyrethroid-susceptible, p-r: pyrethroid-resistant.
The essential oil of spearmint [Mentha spicata L. (Lamiaceae)] leaves also showed larvicidal activity (LC₅₀ 56.08 μg/mL). The main constituents were carvone (11) (48.6%), cis-carveol (12, 21.3%) and limonene (13, 11.3%) [72]. Another spice with larvicidal activity was turmeric [Curcuma longa L. (Zingiberaceae)] whose rhizome essential oil demonstrated LC₅₀ 65.51 μg/mL [62]. Similarly, Porophyllum ruderale (Jacq.) Cass. (Asteraceae) leaves essential oil, a herb used for seasoning food, showed LC₅₀ 60.9 μg/mL for L3 larvae and LC₅₀ 72.3 μg/mL for L4. The main metabolite identified was β-ocimene (14, 94%) [75].

Two other species exhibited very similar LC₅₀ values (ca. 93 μg/mL): clove [Syzygium aromaticum (L.) Merr. & L.M. Perry (Myrtaceae)] against L4 larvae and Tanacetum argenteum Pluchea carolinensis (Jack.) G. (Asteraceae) demonstrated repellency (36.6%) at 1.0% concentration and Pellet. (Lamiaceae); Bauhinia pulchella (Boiss. & Buhse and galbaniflua (L.) Sprague (Apiaceae); Porophyllum ruderale (Jack.) G. (Asteraceae) leaves showed poor activity: larvae (LC₅₀ 240 μg/mL) and leaves (LC₅₀ > 400 μg/mL). The essential oil major compounds were: cedrol (16, 53.0%) and α-pinene (4, 25.6%, wood), and α-pinene (4, 35.9%) and p-cymene (17, 16.7%, leaves) [71]. The results suggest that compound synergy is important for essential oil larvicidal activity as isolated compounds showed lower toxicity, with the exception of p-cymene [71].

Alpinia purpurata (Viell.) K. Schum. (Zingiberaceae) and Croton rhamnifoliioides Pax & K. Hoffm. (Euphorbiaceae) demonstrated toxicity against L4 larvae and oviposition deterrent effect. The LC₅₀ of A. purpurata essential oil was 71.5 μg/mL (pink flowers) and 80.7 μg/mL (red flowers) [67], while the LC₅₀ for C. rhamnifolioides was 89.0 μg/mL (fresh leaves) and 122.3 μg/mL (stored leaves) [70].

Other species, such as Baccharis reticulata DC. (Asteraceae); Piper aduncum L. (Piperaceae) and Pinus sylvestris L. (Pinaceae) showed weak larvicidal activities (LC₅₀ 100.4-290.0 μg/mL) [68,73,74]. Bauhinia pulchella Benth. (Fabaceae) displayed weak activity (105.9 μg/mL) whereas Bauhinia ungulata L. (Fabaceae) was active (75.1 μg/mL) [69] and Pimenta dioica (L.) Merr. (Myrtaceae) was investigated for both larvicidal (weak activity, LC₅₀ 104.4 μg/mL) [54] and adulticidal action (very active, LC₅₀ 16.6 μg/mL) [24].

The essential oil of Sphaeranthus indicus L. (Asteraceae) leaves showed poor activity: larvae (LC₅₀ 140 μg/mL), adult (800 μg/mL for 100% mortality) and repellent (200 μg/mL). This essential oil showed low toxicity (1500 μg/mL) to a non-target aquatic predator [Toxorhynchites splendens (Diptera: Culicidae)] [77]. Similarly, the essential oil of rosemary [Rosmarinus officinalis L. (Lamiaceae)] was poor active when incorporated into a nanoemulsion and tested for larvicidal activity. The mortality of L3 larvae at 250 μg/mL of product was 80% at 24 h and 90% at 48 h [76].

Seo et al. (2012) investigated the activity of 7 plant species essential oils against L3 larvae at 50 μg/mL and 100 μg/mL. Mortality ranged from 80 to 100% after 48 h. The species tested were Ferula galbaniflua Boiss. & Buhse and Trachyspermum ammi (L.) Sprague (Apiaceae); Hyssopus officinalis L. and Pogostemon patchouli Pellet. (Lamiaceae); Larix europea Lam. & A. DC. (Pinaceae); Myroxylon Pereirae (Royle) Klotzsch (Fabaceae), and Pelargonium graveolens L’Hér. ex Aiton (Geraniaceae) [45]. Additional LC₅₀ data is required to determine the degree of activity against Ae. aegypti larvae.

Repellent activity was reported for essentials oils of Acantholippia seriphioides (A. Gray) Moldenke (Verbenaceae) and Alysoya citriodora Palau (Verbenaceae); Baccharis spartioides (Hook. & Arn.) Remy (Asteraceae) and Tagetes minuta L. (Asteraceae), and Minhostachys mollis Griseb and Rosmarinus officinalis. All of the aforementioned demonstrated 100% repellency (12.5–50%) [63]. In another study, Pluchea carolinensis (Jack.) G. (Asteraceae) demonstrated repellency (36.6%) at 1.0% concentration and irritation (62.2%) at 0.1% concentration [79].

The results listed and discussed in this section clearly suggest that essential oils present a promising alternative to develop an effective natural and potentially more eco-friendly insecticide for the control of Ae. aegypti, especially during the larval phase. The challenges for these materials are to improve
solubility in water and prolong the insecticidal effect. It is also important to understand the synergism and/or antagonism of their constituents, together with the optimum ratio.

5. Organic/Aqueous Extracts

Concerning organic/aqueous extracts, the plant families with the highest number of species tested against *Ae. aegypti* larvae were Fabaceae, Asteraceae, Piperaceae and Euphorbiaceae. Similarly, as described by Isman (2015), India was the country with the most publications in this field, followed by Brazil [14].

Of the 20 plant species, at least one organic/aqueous extract showed high larvicidal activity (*LC₅₀* < 50 µg/mL); 12 were active (*LC₅₀* 50–100 µg/mL) and 26 had weak activity (*LC₅₀* > 100 µg/mL). Nevertheless, these values can change significantly after formulation in a similar way to essential oils, as described in Section 8 “Limitations and/or Expectations of Plant Natural Product Insecticidal Applications”.

Figure 4 details the chemical structures of the secondary metabolites identified in the organic extracts.

![Chemical Structures](image)

**Figure 4.** Secondary metabolites identified in organic extracts with insecticidal activity against *Ae. aegypti*. (A) Fatty acid and derivatives, (B) Diterpenes and triterpenes and (C) Others.

Tables 3 and 4 summarise the scientific literature selected for the discussion of insecticidal activities of organic/aqueous extracts against *Ae. aegypti* mosquito. Table 3 describes larvicidal activities, while Table 4 describes adulticidal, pupicidal, ovicidal, repellent and oviposition activities.
Table 3. Larvicidal activity of organic/aqueous extracts against the *Ae. aegypti* mosquito.

| Plant Species                        | Family       | Country        | Part Used | Extraction Solvent | Larval Stage | Mortality | Time (h) | Reference |
|--------------------------------------|--------------|----------------|-----------|--------------------|--------------|-----------|----------|----------|
| *Acacia nilotica* (L.) Delile        | Fabaceae     | India          | Seed pod  | n-Hexane           | L4           | 169.25    | 201.62   | 24 [58]  |
|                                      |              |                |           | Benzene            | L4           | 45.32     | 99.32    | 24 [58]  |
|                                      |              |                |           | Chloroform         | L4           | 158.13    | 198.24   | 24 [58]  |
|                                      |              |                |           | Ethyl acetate      | L4           | 59.12     | 75.82    | 24 [58]  |
|                                      |              |                |           | Acetone            | L4           | 103.68    | 162.03   | 24 [58]  |
|                                      |              |                |           | n-Hexane           | L4           | 202.15    | 476.57   | 24 [58]  |
|                                      |              |                |           | Chloroform         | L4           | 182.58    | 460.83   | 24 [80]  |
| *Acalypha alnifolia* Klein ex Willd. | Euphorbiaceae| India          | Leaves    | Ethyl acetate      | L4           | 160.35    | 440.78   | 24 [80]  |
|                                      |              |                |           | Acetone            | L4           | 146.07    | 415.38   | 24 [80]  |
| *Aristolochia bracteata* Retz.       | Aristolochiaceae | India        | Leaves    | Methanol           | L3           | 114.89    | 216.24   | 24 [81]  |
| *Artemisia herba-alba* Asso           | Asteraceae   | Saudi Arabia   | Leaves    | Water              | L4—India     | 117.18    | 227.63   | 24 [82]  |
|                                      |              |                |           | Water + AgNP       | L4—Saudi Arabia | 614.52    | 1273.33  | 24 [82]  |
|                                      |              |                |           | Water              | L4—India     | 10.70     | 21.24    | 24 [82]  |
|                                      |              |                |           | Water + AgNP       | L4—Saudi Arabia | 33.58     | 57.0     | 24 [82]  |
| *Boenninghausenia albiflora* (Hook.) Rchb. ex Meisn. | Rutaceae     | India          | Leaves    | Petroleum ether    | L4           | 125.0     | 190.0    | ND [83]  |
| *Buddleja polyspachya* Fresen.       | Buddlejaceae | Saudi Arabia   | Flowers   | n-Butanol          | L1           | ND        | ND       | ND [84]  |
| *Caesalpinia pulcherrima* (L.) Sw.   | Fabaceae     | India          | Leaves    | Ethyl acetate      | L3           | 144.67    | 276.99   | 24 [85]  |
| *Cassia fistula* L.                  | Fabaceae     | India          | Leaves    | Benzene            | L3           | 136.36    | 272.15   | 24 [85]  |
|                                      |              |                |           | Methanol           | L3           | 10.69     | 20.47    | 24 [86]  |
|                                      |              |                |           | Benzene            | L3           | 18.27     | 35.67    | 24 [86]  |
| *Catharanthus roseus* (L.) G. Don    | Apocynaceae  | India          | Leaves    | Petroleum ether    | L4           | 145.0     | 255.0    | 24 [83]  |
| *Cinnamomus fragrans* Baill.         | Canellaceae  | Madagascar     | Root Bark | Methanol           | L1           | 32.5      | ND       | 24 [87]  |
| *Citrus colocynthis* (L.) Schrad.   | Cucurbitaceae| India          | Leaves    | Petroleum ether    | L4           | 74.57     | 538.30   | 24 [88]  |
| *Cunninghamia konishii* Hayata       | Taxodiaceae  | Taiwan         | Leaves    | Ethanol            | L4           | 240.0     | >400.0   | 24 [73]  |
|                                      |              |                |           | Ethanol            | L3           | 30.0      | 91.0     | 24 [89]  |
| *Dalbergia brasiliensis* Vogel       | Fabaceae     | Brazil         | Leaves    | n-Hexane Fraction  | L3           | 44.0      | 81.0     | 24 [89]  |
|                                      |              |                |           | Chloroform Fraction| L3           | 33.0      | 75.0     | 24 [89]  |
|                                      |              |                |           | Ethyl acetate     | L3           | 24.0      | 66.0     | 24 [89]  |
|                                      |              |                |           | Ethanol            | L3           | 32.0      | 71.0     | 24 [89]  |
|                                      |              |                |           | n-Hexane Fraction  | L3           | 31.0      | 72.0     | 24 [89]  |
|                                      |              |                |           | Chloroform Fraction| L3           | 25.0      | 50.0     | 24 [89]  |
| Plant Species                        | Family      | Country     | Part Used   | Extraction Solvent | Larval Stage | Mortality | Time (h) | Reference |
|-------------------------------------|-------------|-------------|-------------|--------------------|--------------|-----------|----------|-----------|
|                                     |             |             |             |                    | L3           | LC₅₀ (ppm)|          |           |
|                                     |             |             |             |                    | L₉₀ (ppm)    |           |          |           |
|                                     |             |             |             |                    |              | LC₅₀ (ppm)| LC₉₀ (ppm)| Reference |
| **Echinops transiliensis** Golok.   | Asteraceae  | Kazakhstan  | Root        | Ethyl acetate      | L₃           | 28.0      | 93.0     | [89]      |
|                                     |             |             |             | Fraction           |              |           |          |           |
|                                     |             |             |             | Dichlorometane     | L₃           | 3.21      | 6.81     | [90]      |
|                                     |             |             |             | Benzene            | L₃           | 151.38    | 274.34   | [91]      |
|                                     |             |             |             | n-Hexane           | L₃           | 165.10    | 297.70   | [91]      |
| **Eclipta alba** (L.) Hassk.        | Asteraceae  | India       | Leaves      | Ethyl acetate      | L₃           | 154.88    | 286.61   | [91]      |
|                                     |             |             |             | Methanol           | L₃           | 127.64    | 245.73   | [91]      |
|                                     |             |             |             | Chloroform         | L₃           | 146.28    | 274.42   | [91]      |
| **Eratodium coronaria** (Jacq.) Stapf. | Apocynaceae | India       | Leaves      | Ethyl acetate      | L₃           | 97.53     | 179.37   | [85]      |
|                                     |             |             |             | Benzene            | L₃           | 89.59     | 166.04   | [85]      |
| **Eupatorium odoratum** L.          | Asteraceae  | India       | Leaves      | Petroleum ether    | L₄           | 155.0     | 290.0    | ND [83]   |
| **Euphorbia hirta** L.              | Euphorbiaceae | India       | Leaves      | Petroleum ether    | L₄           | 272.36    | 703.76   | [92]      |
| **Euphorbia tirucalli** L.          | Euphorbiaceae | India       | Stem bark   | Petroleum ether    | L₄           | 4.25      | 13.14    | [92]      |
|                                     |             |             |             | Methanol           | L₂           | 56.54     | 109.29   | [93]      |
|                                     |             |             |             | Methanol           | L₃           | 70.29     | 137.23   | [93]      |
|                                     |             |             |             | Methanol           | L₄           | 80.85     | 169.58   | [93]      |
|                                     |             |             |             | Benzene            | L₂           | 108.95    | 227.13   | [93]      |
| **Ficus benghalensis** L.           | Moraceae    | India       | Leaves      | Benzene            | L₃           | 116.09    | 235.54   | [93]      |
|                                     |             |             |             | Benzene            | L₄           | 159.15    | 430.91   | [93]      |
|                                     |             |             |             | Acetone            | L₂           | 189.11    | 444.42   | [93]      |
|                                     |             |             |             | Acetone            | L₃           | 244.41    | 573.52   | [93]      |
|                                     |             |             |             | Acetone            | L₄           | 288.10    | 668.71   | [93]      |
| **Gardenia ternifolia** Schumach. & Thonn. | Rubiaceae | Kenya       | Leaves      | Acetone            | L₂           | 83.31     | ND       | [94]      |
|                                     |             |             |             | Methanol           | L₂           | 32.01     | ND       | [94]      |
| **Helicteres velutina** K. Schum.   | Malvaceae   | Brazil      | Root        | Ethanol 90%         | L₄           | 171.68    | 403.61   | [95]      |
|                                     |             |             | Stem        | Ethanol 90%         | L₄           | 138.90    | 319.37   | [95]      |
|                                     |             |             |             | Petroleum ether    | L₂           | 40.64     | 65.49    | [96]      |
|                                     |             |             |             | Chloroform         | L₂           | 69.22     | 132.95   | [96]      |
|                                     |             |             |             | Ethyl acetate      | L₂           | 70.65     | 93.11    | [96]      |
|                                     |             |             |             | Methanol           | L₂           | 74.70     | 135.07   | [96]      |
|                                     |             |             |             | Acetone            | L₂           | 97.07     | 198.99   | [96]      |
|                                     |             |             |             | Petroleum ether    | L₃           | 91.55     | 162.09   | [96]      |
| **Heracleum rigens** Wall.          | Apioaceae   | India       | Seed        | Chloroform         | L₃           | 114.25    | 179.99   | [96]      |
|                                     |             |             |             | Ethyl acetate      | L₃           | 143.48    | 207.45   | [96]      |
|                                     |             |             |             | Methanol           | L₃           | 195.57    | 348.56   | [96]      |
|                                     |             |             |             | Acetone            | L₃           | 234.77    | ND       | [96]      |
|                                     |             |             |             | Petroleum ether    | L₄           | 113.69    | 171.12   | [96]      |
| Plant Species                  | Family      | Country    | Part Used | Extraction Solvent | Larval Stage | Mortality | Time (h) | Reference |
|-------------------------------|-------------|------------|-----------|--------------------|--------------|-----------|----------|-----------|
| Hypericum japonicum Thunb.   | Hypericaceae| India      | Whole plant| Chloroform         | L4           | LC_50     | 144.64   | 24        | [96]      |
|                               |             |            |           | Ethyl acetate      | L4           | LC_50     | 165.43   | 24        | [96]      |
|                               |             |            |           | Methanol           | L4           | LC_50     | 231.26   | 24        | [96]      |
|                               |             |            |           | Acetone            | L4           | LC_50     | 308.65   | 24        | [96]      |
|                               |             |            |           | Acetone            | L4           | LC_90     | 13.15    | 24        | [97]      |
|                               |             |            |           | n-Hexane           | L4           | LC_90     | 9.63     | 24        | [97]      |
|                               |             |            |           | Petroleum ether    | L4           | LC_90     | 8.27     | 24        | [97]      |
|                               |             |            |           | Methanol           | L4           | LC_90     | 7.37     | 24        | [97]      |
| Jatropha curcas L.            | Euphorbiaceae| India      | Leaves    | Petroleum ether    | L4           | LC_90     | 8.79     | 24        | [92]      |
|                               |             |            | Root      | Petroleum ether    | ND           | LC_90     | 44.75    | 24        | [98]      |
| Linonia acidissima L.         | Rutaceae    | India      | Leaves    | n-Hexane—Purified  | L3           | LC_90     | 4.11 to 23.53 | ND     | 24        | [99]      |
| Lonchocarpus urucu Killip & A.C. Sm. | Fabaceae | Brazil     | Medulla   | Methanol           | L4           | LC_90     | 33.32    | 24        | [100]     |
|                               |             |            | Root      | Methanol           | L4           | LC_90     | 17.60    | 24        | [100]     |
|                               |             |            | Bark Root | Methanol           | L4           | LC_90     | 97.03    | 24        | [100]     |
| Maytenus oblongata Reissek    | Celastraceae| French Guiana | Bark       | Ethyl acetate      | L3/L4        | LC_90     | 74.40    | ND        | 24        | [101]     |
| Millettia pachycarpa Benth.   | Fabaceae    | India      | Root      | Ethanol            | L3           | LC_90     | 98.47    | ND        | 24        | [102]     |
|                               |             |            | Bark      | Benzene            | L3           | LC_90     | 97.03    | 24        | [103]     |
|                               |             |            | Root      | Chloroform         | L3           | LC_90     | 88.20    | 24        | [103]     |
|                               |             |            | Root      | Ethyl acetate      | L3           | LC_90     | 72.77    | 24        | [103]     |
|                               |             |            | Root      | Methanol           | L3           | LC_90     | 64.58    | 24        | [103]     |
|                               |             |            | Root      | Methanol           | L4           | LC_90     | 199.14   | 24        | [103]     |
|                               |             |            | Root      | Methanol           | L1           | LC_90     | 162.03   | 24        | [103]     |
|                               |             |            | Root      | Methanol           | L2           | LC_90     | 194.11   | 24        | [103]     |
|                               |             |            | Root      | Methanol           | L3           | LC_90     | 240.10   | 24        | [103]     |
|                               |             |            | Root      | Methanol           | L4           | LC_90     | 273.90   | 24        | [103]     |
|                               |             |            | Root      | Methanol + ZnO NP  | L1           | LC_90     | 3.44     | 24        | [103]     |
|                               |             |            | Root      | Methanol + ZnO NP  | L2           | LC_90     | 5.25     | 24        | [103]     |
|                               |             |            | Root      | Methanol + ZnO NP  | L3           | LC_90     | 8.02     | 24        | [103]     |
|                               |             |            | Root      | Methanol + ZnO NP  | L4           | LC_90     | 10.28    | 24        | [103]     |
| Mirabilis jalapa L.           | Nyctaginaceae| India      | Leaves    | Chloroform         | L3           | LC_90     | 88.20    | 24        | [103]     |
|                               |             |            | Leaves    | Ethyl acetate      | L3           | LC_90     | 72.77    | 24        | [103]     |
|                               |             |            | Leaves    | Methanol           | L3           | LC_90     | 64.58    | 24        | [103]     |
|                               |             |            | Leaves    | Methanol           | L4           | LC_90     | 199.14   | 24        | [103]     |
|                               |             |            | Leaves    | Methanol           | L1           | LC_90     | 162.03   | 24        | [103]     |
|                               |             |            | Leaves    | Methanol           | L2           | LC_90     | 194.11   | 24        | [103]     |
|                               |             |            | Leaves    | Methanol           | L3           | LC_90     | 240.10   | 24        | [103]     |
|                               |             |            | Leaves    | Methanol           | L4           | LC_90     | 273.90   | 24        | [103]     |
|                               |             |            | Leaves    | Methanol + ZnO NP  | L1           | LC_90     | 3.44     | 24        | [103]     |
|                               |             |            | Leaves    | Methanol + ZnO NP  | L2           | LC_90     | 5.25     | 24        | [103]     |
|                               |             |            | Leaves    | Methanol + ZnO NP  | L3           | LC_90     | 8.02     | 24        | [103]     |
|                               |             |            | Leaves    | Methanol + ZnO NP  | L4           | LC_90     | 10.28    | 24        | [103]     |
|                               |             |            | Leaves    | Ethanol            | L4 (p-s)     | LC_90     | 75.45    | 24        | [103]     |
|                               |             |            | Leaves    | Ethyl acetate      | L1           | LC_90     | 8.0      | ND        | 24        | [104]     |
|                               |             |            | Leaves    | Petroleum ether    | L4           | LC_90     | 180.0    | 24        | [83]      |
|                               |             |            | Flowers   | Petroleum ether    | L4           | LC_90     | 123.60   | 24        | [60]      |
|                               |             |            | Flowers   | Ethanol            | L4           | LC_90     | 75.45    | 24        | [60]      |
|                               |             |            | Flowers   | Ethanol            | L4           | LC_90     | 75.45    | 24        | [60]      |
|                               |             |            | Leaves    | Acetone            | L4           | LC_90     | 425.94   | ND        | 24        | [105]     |
|                               |             |            | Leaves    | Chloroform         | L4           | LC_90     | 150.40   | ND        | 24        | [105]     |
| Plant Species                | Family       | Country | Part Used | Extraction Solvent | Larval Stage | Mortality | Reference |
|-----------------------------|--------------|---------|-----------|--------------------|--------------|-----------|-----------|
| **Ormosia arborea Vell**    | Fabaceae     | Brazil  | Leaves    | Ethyl acetate      | L4           | 350.78    | [105]     |
|                            |              |         |           | n-Hexane           | L4           | 575.26    | [105]     |
|                            |              |         |           | Methanol           | L4           | 175.67    | [105]     |
|                            |              |         |           | Ethanol            | L3           | 238.0     | [106]     |
|                            |              |         |           | Ethanol            | L3           | 111.0     | [106]     |
|                            |              |         |           | n-Hexane           | L3           | 228.13    | [107]     |
|                            |              |         |           | Chloroform         | L3           | 209.72    | [107]     |
| Orthosiphon thymiflorus (Roth) Sleesen | Labiatae     | India   | Leaves    | Ethyl acetate      | L3           | 183.35    | [107]     |
|                            |              |         |           | Acetone            | L3           | 163.55    | [107]     |
|                            |              |         |           | Methanol           | L3           | 149.96    | [107]     |
| Pedilanthus tithymaloides (L.) Poit. | Euphorbiaceae | India   | Leaves    | Petroleum ether    | L4           | 55.26     | [92]      |
|                            |              |         |           | Methanol           | L3           | 22.10     | [108]     |
|                            |              |         |           | n-Hexane           | L3           | 34.39     | [108]     |
|                            |              |         |           | Acetone            | L3           | 56.76     | [108]     |
| *Phyllanthus amarus* Schumach. & Thonn. | Euphorbiaceae | India   | Leaves    | Petroleum ether    | L4           | 90.92     | [92]      |
| *Piper aduncum* L.         | Piperaceae   | Brazil  | Leaves    | n-Hexane           | L3           | 342.0     | [106]     |
|                            |              |         |           | Chloroform         | L3           | 192.0     | [106]     |
| *Piper hispidum* Sw.      | Piperaceae   | Brazil  | Leaves    | Ethanol            | L3           | 169.0     | [106]     |
|                            |              |         |           | Chloroform         | L3           | 567.0     | [106]     |
| *Piper longum* L.         | Piperaceae   | Thailand| Fruits    | Ethanol            | L4           | 2.23      | [109]     |
|                            |              |         |           | Ethanol            | L3/L4        | 71.25     | [110]     |
| *Piper nigrum* L.         | Piperaceae   | Philippines | Peppercorns | Ethanol-Fraction 1A | L3/L4        | 17.10     | [110]     |
|                            |              |         |           | Ethanol-Fraction 1B| L3/L4        | 18.10     | [110]     |
| *Piper ribesoides* Wall.  | Piperaceae   | Thailand| Wood      | Ethanol            | L4           | 8.13      | [109]     |
| *Piper sarmentosum* Roxb. ex Hunt. | Piperaceae   | Thailand| Whole plant | Ethanol            | L4           | 4.06      | [109]     |
|                            |              |         |           | Ethanol            | L3           | 155.78    | [111]     |
|                            |              |         |           | Ethyl acetate      | L3           | 162.36    | [111]     |
|                            |              |         |           | Chloroform         | L3           | 169.08    | [111]     |
|                            |              |         |           | Benzene            | L3           | 176.02    | [111]     |
|                            |              |         |           | n-Hexane           | L3           | 185.14    | [111]     |
|                            |              |         |           | Methanol           | L3           | 193.66    | [111]     |
|                            |              |         |           | Ethyl acetate      | L3           | 215.63    | [111]     |
| *Pithecellobium Dulce* (Roxb.) Benth. | Fabaceae     | India   | Seeds     | Chloroform         | L3           | 240.39    | [111]     |
Table 3. Cont.

| Plant Species                          | Family           | Country | Part Used | Extraction Solvent | Larval Stage | Mortality   | Time (h) | Reference |
|----------------------------------------|------------------|---------|-----------|--------------------|--------------|-------------|----------|-----------|
| Scoparia dulcis L.                     | Plantaginaceae   | Brazil  | Leaves    | Ethanol 90%        | L3           |LC₅₀ (ppm)  | 259.42   | 24        | [111]     |
|                                        |                  |         |           |                    | L3           | LC₉₀ (ppm)  | 489.41   |           |           |
|                                        |                  |         |           |                    | L4           |            | 281.18   | 24        | [111]     |
|                                        |                  |         |           |                    | L4           |            | 516.33   |           |           |
| Solanum nigrum L.                     | Solanaceae       | India   | Fruit     | Water              | L3/L4        |LC₅₀ (ppm)  | 83.43    | 24        | [112]     |
|                                        |                  |         |           |                    | L3/L4        | LC₉₀ (ppm)  | 158.83   |           |           |
|                                        |                  |         |           |                    | L3/L4        |            | 931.0    |           |           |
| Solanum variabile Mart.               | Solanaceae       | Brazil  | Leaves    | n-Hexane           | L3/L4        |LC₅₀ (ppm)  | 17.65    | 24        | [113]     |
|                                        |                  |         |           |                    | L3/L4        | LC₉₀ (ppm)  | 65.22    |           |           |
|                                        |                  |         |           |                    | L3/L4        |            | 284.0    |           |           |
| Solanum xanthocarpum Schrad. & J.C.   | Solanaceae       | India   | Fruit     | Methanol           | L1           |LC₅₀ (ppm)  | 170.91   | 24        | [114]     |
| Wendl.                                |                  |         |           |                    | L1           | LC₉₀ (ppm)  | 320.62   |           |           |
|                                        |                  |         |           |                    | L1           |            | 24       |           |           |
|                                        |                  |         |           |                    | L1           |            | 24       |           |           |
|                                        |                  |         |           |                    | L1           |            | 24       |           |           |
| Spermacoce latifolia Aubl.            | Rubiaceae        | Brazil  | Leaves    | Methanol           | L2           |LC₅₀ (ppm)  | 195.07   | 24        | [114]     |
|                                        |                  |         |           |                    | L2           | LC₉₀ (ppm)  | 366.48   |           |           |
|                                        |                  |         |           |                    | L2           |            | 24       |           |           |
|                                        |                  |         |           |                    | L2           |            | 24       |           |           |
| Tagetes patula L.                     | Asteraceae       | Brazil  | Seeds     | Acetone            | L4           |LC₅₀ (ppm)  | 625.0    | 24        | [106]     |
|                                        |                  |         |           |                    | L4           | LC₉₀ (ppm)  | 1122.0   |           |           |
|                                        |                  |         |           |                    | L4           |            | 24       |           |           |
|                                        |                  |         |           |                    | L4           |            | 24       |           |           |
| Turnera ulmifolia L.                  | Turneraceae      | Brazil  | Leaves    | Ethanol 50%        | L3           |LC₅₀ (ppm)  | 25.46    | 48        | [115]     |
| Valeriana hardwickii Wall.            | Valerianaceae    | India   | Leaves    | Petroleum ether    | L4           | LC₉₀ (ppm)  | 15.74    | 48        | [115]     |
|                                        |                  |         |           |                    | L4           |            | ND       |           |           |
|                                        |                  |         |           |                    | L4           |            | ND       |           |           |
| Ventilago madraspatana Gaertn.        | Rhammnaceae      | India   | Leaves    | Water + AgNP       | L3           |LC₅₀ (ppm)  | 26.82    | 24        | [112]     |
|                                        |                  |         |           |                    | L3           | LC₉₀ (ppm)  | ND       |           |           |
|                                        |                  |         |           |                    | L3           |            | 24       |           |           |
| Zeuxine gracilis (Berda) Bl.          | Orchidaceae      | India   | Leaves    | Water + AgNP       | L3           |LC₅₀ (ppm)  | 10.39    | 24        | [116]     |
|                                        |                  |         |           |                    | L3           | LC₉₀ (ppm)  | 23.58    |           |           |

LC₅₀ lethal concentration required to kill 50% of the larval population, LC₉₀ lethal concentration required to kill 90% of the larval population, ND not described, p-s pyrethroid-susceptible, AgNP silver nanoparticle, ZnONP zinc oxide nanoparticle.
Table 4. Adulticidal, pupicidal, ovicidal, repellent and oviposition activities of organic/aqueous extracts against the *Ae. aegypti* mosquito.

| Plant Species           | Family          | Country       | Part Used         | Extraction Solvent | Activity          | Results                              | Time (h) | Reference |
|-------------------------|-----------------|---------------|-------------------|--------------------|-------------------|--------------------------------------|----------|-----------|
| *Alpinia purpurata*     | Zingiberaceae   | Brazil        | Red Flowers       | Water              | Oviposition       | Oviposition disruptive effect         | 24       | [67]      |
|                         |                 |               | Pink Flowers      | Methanol           | Oviposition       | Zero hatchability at 240 ppm          | 48       | [81]      |
| *Aristolochia bracteata*| Aristolochiaceae| India         | Leaves            | Methanol           | Repellent         | 100% of repellency at 6 mg/cm²²      | 3        | [81]      |
| *Artemisia herba-alba*  | Asteraceae      | Saudi Arabia  | Leaves            | Water              | Adulticide        | LC₅₀ = 327.15 µg/mL                  | 24       | [82]      |
|                         |                 |               |                   |                    | from India        | LC₃₀ 779.98 µg/mL                   |          |           |
|                         |                 |               |                   | Water              | Adulticide        | LC₉₀ 450.21 µg/mL                   | 24       | [82]      |
|                         |                 |               |                   |                    | from India        | LC₉₀ 1153.18 µg/mL                  |          |           |
| *Buddleja polystachya*  | Buddlejaceae    | Saudi Arabia  | Flowers           | Methanol           | Adulticide         | LC₃₀ = 39.88 µg/mL                  | 24       | [82]      |
|                         |                 |               | Aerial parts      | Ethanol            | Adulticide         | LC₉₀ 25.62 µg/mL                    |          |           |
| *Caesalpinia pulcherrima*| Fabaceae       | India         | Leaves            | Ethyl acetate      | Ovicidal          | Zero hatchability at 450 ppm         | 48       | [85,117]  |
|                         |                 |               |                   | Ethyl acetate      | Repellent         | 100% of repellency at 5 mg/cm²²      | 1.5      | [85,117]  |
| *Cardiospermum hallocabrum*| Sapindaceae  | India         | Leaves            | Benzene            | Ovicide           | Zero hatchability at 375 ppm         | 48       | [85,117]  |
|                         |                 |               |                   | Benzene            | Repellent         | 100% of repellency at 5 mg/cm²²      | 2        | [85,117]  |
| *Cassia fistula*        | Fabaceae        | India         | Leaves            | Benzene            | Ovicide           | Zero hatchability at 140 ppm         | 48       | [86]      |
| *Cinnamomus fragrans*   | Canellaceae     | Madagascar    | Root barks        | Methanol           | Adulticide        | LC₃₀ 0.17 µg/mg female               | 24       | [87]      |
|                         |                 |               |                   | Methanol           | Repellent         | 80% of repellency at 20.8 µg/cm²    | 3        | [87]      |
| Plant Species          | Family             | Country     | Part Used | Extraction Solvent | Activity | Results                          | Time (h) | Reference |
|------------------------|--------------------|-------------|-----------|--------------------|----------|----------------------------------|----------|-----------|
| *Coccinia indica* Wight & Arn. | Cucurbitaceae    | India       | Leaves    | Benzene            | Ovicide  | Zero hatchability at 250 ppm     | 48       | [119]     |
|                        |                    |             |           | n-Hexane           | Repellent| 100% of repellency at 300 ppm   | 48       | [119]     |
|                        |                    |             |           | n-Hexane           | Repellent| Zero hatchability at 1 mg/cm²    | 2.5      | [119]     |
|                        |                    |             |           | Ethyl acetate      | Ovicide  | Zero hatchability at 250 ppm     | 48       | [119]     |
|                        |                    |             |           | Ethyl acetate      | Repellent| 100% of repellency at 2.5 mg/cm²| 2.5      | [119]     |
|                        |                    |             |           | Methanol           | Ovicide  | Zero hatchability at 200 ppm     | 48       | [119]     |
|                        |                    |             |           | Methanol           | Repellent| 100% of repellency at 5 mg/cm²  | 3.5      | [119]     |
|                        |                    |             |           | Chloroform         | Ovicide  | Zero hatchability at 250 ppm     | 48       | [119]     |
|                        |                    |             |           | Chloroform         | Repellent| 100% of repellency at 2.5 mg/cm²| 2.5      | [119]     |
| *Eclipta alba* (L.) Hassk. | Asteraceae        | India       | Leaves    | Ethyl acetate      | Ovicide  | Zero hatchability at 350 ppm     | 48       | [119]     |
|                        |                    |             |           | Methanol           | Ovicide  | Zero hatchability at 300 ppm     | 48       | [91]      |
|                        |                    |             |           | Chloroform         | Ovicide  | Zero hatchability at 350 ppm     | 48       | [119]     |
|                        |                    |             |           | Methanol           | Ovicide  | Zero hatchability at 200 ppm     | 48       | [117]     |
|                        |                    |             |           | Methanol           | Repellent| 100% of repellency at 5 mg/cm²  | 3        | [117]     |
| *Ervatania coronaria* (Jacq.) Stapf. | Apocynaceae    | India       | Leaves    | Ethyl acetate      | Ovicide  | Zero hatchability at 300 ppm     | 48       | [117]     |
|                        |                    |             |           | Ethyl acetate      | Repellent| 100% of repellency at 5 mg/cm²  | 2        | [117]     |
|                        |                    |             |           | Benzene            | Ovicide  | Zero hatchability at 250 ppm     | 48       | [117]     |
|                        |                    |             |           | Benzene            | Repellent| 100% of repellency at 5 mg/cm²  | 2.5      | [117]     |
| *Limonia acidissima* L. | Rutaceae          | India       | Leaves    | n-Hexane—Purified fractions | Ovicide  | Zero hatchability at 10 ppm      | 120      | [99]      |
|                        |                    |             |           | n-Hexane—Purified fractions | Pupicide | LC₅₀ 4.19—39.48 µg/mL            | 24       | [99]      |
| *Mentha piperita* L.  | Lamiaceae         | India       | Whole plant| Methanol           | Repellent| Zero hatchability at 200 ppm     | ND       | [120]     |
|                        |                    |             | Root      | Ethanol            | Ovicide  | Repellency                       | ND       | [102]     |
| *Milletia pachycarpa* Benth. | Fabaceae         | India       | Root      | Methanol           | Pupicide | LC₅₀ 803.52 µg/mL                | 24       | [53]      |
|                        |                    |             |           | Methanol           | Pupicide | LC₅₀ 14.63 µg/mL                 | 24       | [53]      |
| *Myristica fragans* Houtt. | Myristicaceae    | India       | Leaves    | Methanol + ZnONP   | Pupicide | LC₅₀ 180.26 µg/mL                | 24       | [53]      |
|                        |                    |             |           | Methanol           | Adulticide| LC₅₀ 368.93 µg/mL                | 24       | [53]      |
|                        |                    |             |           | Methanol + ZnONP   | Adulticide| LC₅₀ 4.6 μg/mg female           | 24       | [104]     |
| *Nerine sarniensis* (L.) Herb. | Amaryllidaceae  | South Africa| Bulbs    | Ethyl acetate      | Adulticide| LC₅₀ 34.2 µg/mL                 | 24       | [53]      |
Table 4. Cont.

| Plant Species                  | Family          | Country   | Part Used | Extraction Solvent | Activity | Results                                      | Time (h) | Reference |
|--------------------------------|-----------------|-----------|-----------|--------------------|----------|----------------------------------------------|----------|-----------|
| Parthenium hysterophorus       | Asteraceae      | India     | Leaves    | Ether              | Repellent| 99.6% of repellency at 1000 ppm              | 48       | [121]     |
|                                |                 |           |           | Ether              | Ovicide  | Zero hatchability at 1000 ppm                | 48       | [121]     |
|                                |                 |           |           | Benzene            | Repellent| 93.8% of repellency at 1000 ppm             | 48       | [121]     |
|                                |                 |           |           | Benzene            | Ovicide  | Zero hatchability at 1000 ppm                | 48       | [121]     |
| Pemphis acidula J.R. Forst. & G. Forst. | Lythraceae | India     | Leaves    | Methanol           | Ovicide  | Zero hatchability at 450 ppm                 | 48       | [108]     |
|                                |                 |           |           | Acetone            | Ovicide  | Zero hatchability at 500 ppm                | 48       | [108]     |
|                                |                 |           |           | Methanol           | Ovicide  | Zero hatchability at 400 ppm                | 48       | [111]     |
| Pithecellobium Dulce (Roxb.) Benth. | Fabaceae       | India     | Leaves    | Ethyl acetate      | Ovicide  | Zero hatchability at 500 ppm                | 48       | [111]     |
|                                |                 |           |           | Chloroform         | Ovicide  | Zero hatchability at 500 ppm                | 48       | [111]     |
|                                |                 |           |           | Benzene            | Ovicide  | Zero hatchability at 600 ppm                | 48       | [111]     |
|                                |                 |           |           | Ethyl acetate      | Ovicide  | Zero hatchability at 625 ppm                | 48       | [111]     |
|                                |                 |           |           | Chloroform         | Ovicide  | Zero hatchability at 750 ppm                | 48       | [111]     |
|                                |                 |           |           | Benzene            | Ovicide  | Zero hatchability at 750 ppm                | 48       | [111]     |
| Solanum xanthocarpum Schrad. & J.C. Wendl. | Solanaceae | India     | Fruit     | Methanol           | Pupicide | LC$_{50}$ 279.52 µg/mL                      | 24       | [114]     |
|                                |                 |           |           |                   |         | LC$_{50}$ 462.10 µg/mL                      |          |           |
|                                |                 |           |           | Water + AgNP       | Ovicide  | Zero hatchability at 120 ppm                | 48       | [112]     |
|                                |                 |           |           | Water + AgNP       | Adulticide | LC$_{50}$ 44.85 µg/mL                     | 24       | [112]     |
|                                |                 |           |           | Water + AgNP       | Adulticide | LC$_{50}$ 334.46 µg/mL                     | 24       | [112]     |
|                                |                 |           |           | Water + AgNP       | Ovicide  | Zero hatchability at 12 ppm                | 48       | [116]     |
|                                |                 |           |           |                   | Adulticide | LC$_{50}$ 27.90 µg/mL                     | 24       | [116]     |
| Zeuxine gracilis (Berda) Bl.    | Orchidaceae     | India     | Leaves    | Water + AgNP       | Ovicide  | LC$_{50}$ = 59.20 µg/mL                    | 24       |           |

LC$_{50}$ lethal concentration required to kill 50% of the mosquito population, LC$_{90}$ lethal concentration required to kill 90% of the mosquito population, ND not described, AgNP silver nanoparticle, ZnONP zinc oxide nanoparticle.
Piper species (Piperaceae) demonstrated LC$_{50}$ ranging from 2.23 to 567 µg/mL for L3 and L4 larval stages [106,109,110]. The most active species extracts were *Piper longum* L. (fruit ethanolic), followed by *P. sarmentosum* (entire plant ethanolic LC$_{50}$ 4.06 µg/mL) and *Piper ribesoides* Wall. (wood LC$_{50}$ 8.13 µg/mL) [109]. *Piper nigrum* L. peppercorn ethanolic extract was active and purified fractions were highly active, with possible toxicity due to oleic acid (18) [110]. *P. aduncum* and *Piper hispidum* Sw. displayed weak activity against L3 larvae (LC$_{50}$ > 150 µg/mL) [106].

An *Echinops transiliensis* Golosk. (Asteraceae) root dichloromethane extract showed strong toxicity against larvae (LC$_{50}$ 3.21 µg/mL). The nine thiophene derivatives isolated showed strong activity (LC$_{50}$ 0.16—19.97 µg/mL) [90]. Similarly, a *Euphorbia tirucalli* L. (Euphorbiaceae) stem bark petroleum ether extract presented LC$_{50}$ 4.25 µg/mL against L4 larvae, while a *Euphorbia hirta* L. leaves extract exhibited weak activity (LC$_{50}$ 272.36 µg/mL) [92].

The *Hypericum japonicum* Thunb. (Hypericaceae) species was also very toxic to mosquito larvae. The organic extracts of the whole plant presented LC$_{50}$ values between 7.37 and 13.15 µg/mL. The methanolic extract proved the most active, its purified fraction displaying LC$_{50}$ 0.95 µg/mL. The major constituents of this active fraction were isopropyl palmitate (19), 2,4-Di-tert-butylphenol (20) and hydrocinnamic acid (21) [97]. Similarly active, the *Nerine sarniensis* (L.) Herb. (Amaryllidaceae) bulb ethyl acetate extract demonstrated toxicity against L1 larvae (LC$_{50}$ 8.0 µg/mL) and adult females (LC$_{50}$ 4.6 µg/mosquito) [104].

Purified fractions of an n-hexane extract of *Limonia acidissima* L. (Rutaceae) leaves showed interesting ovicidal, larvicidal and pupicidal activities. The LC$_{50}$ for L3 larvae ranged from 4.11 to 23.53 µg/mL; for pupae 4.19 to 39.48 µg/mL, and the maximum inhibition of egg hatching was 78.4% at 10 ppm. Bioguided fractionation resulted in the isolation of nilocetin (88) [99].

The biological activity of each plant species extract is specific to the plant part(s) and the polarity of the extraction solvent used. Furthermore, activity can differ significantly for the 4 different larval stages [58,86,89,92–94,96,98,100,108,113,115]. This variation is discussed below.

A *Jatropha curcas* L. (Euphorbiaceae) leaves petroleum ether extract showed LC$_{50}$ 8.79 µg/mL whereas the root ethanolic extract demonstrated less activity (LC$_{50}$ 44.75 µg/mL) [92,98]. A methanolic extract of *Gardenia ternifolia* Schumach. & Thonn. (Rubiaceae) leaves was very active (LC$_{50}$ 32.01 µg/mL) whereas an acetone extract exhibited lower activity (LC$_{50}$ 83.31 µg/mL) [94]. This study exemplifies the effect of different solvents on the toxicity of the same plant part.

n-Hexane, chloroform and acetone extracts of *A. nilotica* seed pods showed weak activity (LC$_{50}$ 103—169 µg/mL), while ethyl acetate was more active (LC$_{50}$ 59.12 µg/mL). Interestingly, a benzene extract demonstrated the most activity (LC$_{50}$ 45.32 µg/mL) [58]. A *Ficus benghalensis* L. (Moraceae) leaves methanolic extract showed activity against L2, L3 and L4 larvae, but the activity was low for benzene and acetone extracts [93]. Another example of solvent variation was an aqueous extract of *Solanum nigrum* L. (Solanaceae) fruits which displayed very low activity (LC$_{50}$ 359.0 µg/mL) against L3/L4 larvae, while higher activity was observed for a hexanic extract (LC$_{50}$ 17.63 µg/mL) [113].

With not so discrepant, but nonetheless different results, a *Pemphis acidula* J.R. Forst. & G. Forst. (Lythraceae) leaves methanolic extract (LC$_{50}$ 22.10 µg/mL) was more active than a benzenic leaves extract (LC$_{50}$ 43.99 µg/mL) [108], while a *Togeetes patula* L. (Asteraceae) seeds acetone extract (LC$_{50}$ 15.74 µg/mL) was more active than the 50% ethanol extract (LC$_{50}$ 25.46 µg/mL) [93]. *P. acidula* extracts also demonstrated complete inhibition of egg hatchability at 500 ppm acetone and 450 ppm methanolic [108].

In addition, different parts of *Lonchocarpus urucu* Killip & A.C. Sm. (Fabaceae) extracted with the same solvent (methanol) showed different toxicity. The root bark extract was more active (LC$_{50}$ 17.6 µg/mL) than the root medulla extract (LC$_{50}$ 33.32 µg/mL) against L4 larvae [100]. The toxicity of *Heracleum rigens* Wall. (Apiaceae) seed extracts was evaluated against different larval stages (LC$_{50}$ 40.64 to 308.65 µg/mL), with the petroleum ether extract the most toxic to all larval stages and acetone the least toxic [96].
Different organic solvent extracts of *Cassia fistula* L. (Fabaceae) leaves were evaluated against the mosquito (larvicide, ovicide and repellent). The methanolic extract was the most active for all activities, notably as a larvicidal (LC$_{50}$ 10.69 µg/mL). Other extracts also demonstrated high activity against larvae: benzene (LC$_{50}$ 18.27 µg/mL) and acetone (LC$_{50}$ 23.95 µg/mL). The non-hatching concentration for eggs ranged from 120 to 160 mg/L and the repellent action (100% at 5 mg/cm$^2$) ranged from 6.0 to 4.3 h [86].

*Dalbergia brasiliensis* Vogel (Fabaceae), commonly known as Jacarandá-da-Bahia in Brazil, is a tree native to the states of Bahia, Minas Gerais, Espírito Santo, Rio de Janeiro and São Paulo. Larvicidal activity of its leaves and trunk bark ethanolic extracts, together with fractions purified by partitioning with n-hexane, ethyl acetate and chloroform, were similar (LC$_{50}$ between 24.0 and 44.0 µg/mL) [89]. Studies using the incorporation of inorganic nanoparticles, such as zinc oxide and silver in plant extracts, have shown an increase in their biological activity. They are generally easy to obtain, inexpensive, not to mention non-toxic to humans and animals [53]. All of the plant extracts described below showed higher larvicidal activity when incorporated into nanoparticles [53,82,116].

An aqueous extract of *Artemisia herba-alba* AssO (Asteraceae) leaves was tested against L4 larvae strains from India and Saudi Arabia. The LC$_{50}$ values were 117.18 µg/mL and 614.54 µg/mL for India and Saudi Arabia larvae, respectively. When the extract was incorporated into silver nanoparticles the activity increased significantly to 10.70 µg/mL and 33.58 µg/mL, respectively. Similar results were observed against adult mosquitoes [82].

Aqueous extracts of *Ventilago madraspatana* Gaertn. (Rhamnaceae) and *Zeuxine gracilis* (Berda) Bl. (Orchidaceae) leaves were also more toxic to egg, larvae and adult mosquitoes when incorporated into silver nanoparticles. No egg hatching was observed at 120 µg/mL and 12 µg/mL, respectively. Corresponding larvicidal (LC$_{50}$ 26.92 µg/mL and 10.39 µg/mL) and adulticidal effective dose activities (44.85 µg/mL and 27.90 µg/mL) were observed [112,116].

The activity of a zinc oxide nanoparticle incorporating a *Myristica fragrans* leaf methanolic extract was compared with the crude extract. The activity of the crude extract against the 4 larvae stages (LC$_{50}$ 162.03 to 273.9 µg/mL) was less than the nanoparticles (LC$_{50}$ 3.44 to 10.28 µg/mL). Similar activity was reported against the pupa (crude extract LC$_{50}$ 359.08 µg/mL and nanoparticles LC$_{50}$ 14.63 µg/mL), and female adult forms (crude extract LC$_{50}$ 180.26 µg/mosquito and nanoparticles LC$_{50}$ 15 µg/mosquito) [53].

The compounds isolated were betulinic acid (22); scopadulcic acid A (23); scopadulcic acid B (24); scopadiol (25); scopadulciol (26) and scopadulin (27) [95].

A methanolic extract of *Cinnamosma fragrans* Baill. (Canellaceae) root bark demonstrated potential as an insecticide acting in different ways: L1 larvae (LC$_{50}$ 52.5 µg/mL), adult (0.17 µg/mg) and 80% repellency at 20.8 µg/cm$^2$ [87]. Similarly, extracts of *Ervatamia coronaria* (Jacq.) Stapf. (Apocynaceae), commonly known as Capre jasmine, were evaluated for different insecticidal applications. L3 larvicides: benzene (LC$_{50}$ 89.59 µg/mL) and ethyl acetate (LC$_{50}$ 97.53 µg/mL) [85]. Ovicide/no hatchability: methanol (200 ppm), benzene (250 ppm) and ethyl acetate (300 ppm) [85,117]. The repellent activity was the same for all extracts (100% repellency at 5 mg/cm$^2$) [85,117].

Different extracts were obtained from *Mirabilis jalapa* L. (Nyctaginaceae) leaves and investigated for their L3 larvicidal activity: methanol (LC$_{50}$ 64.58 µg/mL), ethyl acetate (LC$_{50}$ 72.77 µg/mL), chloroform (LC$_{50}$ 88.20 µg/mL) and benzene (LC$_{50}$ 97.03 µg/mL) [103]. Extracts of three other species obtained from the same plant part with different organic solvents were also evaluated. The methanolic extracts were the most active: *Acalypha alnifolia* Klein ex Willd. (Euphorbiaceae) (L4 instant LC$_{50}$ 128.55–202.15 µg/mL), *Orthosiphon thymiflorus* (Roth) Sleesen (Labiatae) (L3 instant LC$_{50}$ 149.96–228.13 µg/mL) and *Ocimum sanctum* L. (Labiatae) (L4 instant LC$_{50}$ 175.67–425.94 µg/mL) [80,105,107].
Petroleum ether leaf extracts of *Pedilanthus tithymaloides* (L.) Poit. (Euphorbiaceae), *Citrus coloquintsis* (L.) Schrad. (Cucurbitaceae) and *Phyllanthus amarus* Schumach. & Thonn. (Euphorbiaceae) were active against L4 instar, with LC$_{50}$ 55.26 µg/mL, 74.57 µg/mL and 90.92 µg/mL, respectively [88,92]. Similar extracts of *Catharanthus roseus* (L.) G. Don (Apocynaceae), *Eupatorium odoratum* L. (Asteraceae), *Nyctanthes arbor-tristis* L. (Olacaceae), Boenninghausenia albiflora (Hook.) Rchb. ex Meisn. (Rutaceae) and *Valeriana hardwickii* Wall. (Valerianaceae) presented weak activity (LC$_{50}$ > 100 µg/mL) [83].

Larvicidal activity was also reported for *Maytenus oblongata* Reissek (Celastraceae) bark ethyl acetate extract (LC$_{50}$ 74.4 µg/mL) and *Millettia pachycarpa* Benth. (Fabaceae) root ethanol extract (LC$_{50}$ 98.47 µg/mL) [101,102]. The latter also demonstrated ovicidal activity at 200 ppm (100% non-hatchability) [102].

Ethanol, n-hexane and n-butanol extracts of flowers and aerial parts of *Buddleja polystachya* Fresen. (Buddlejaceae) were evaluated for adulticidal activity at 5 µg/mosquito: the most active was n-hexane aerial parts (100% mortality), followed by n-hexane flowers (96.7% mortality), ethanol aerial parts (90% mortality) and ethanol flowers (83.3% mortality). Only the n-butanol flower extract was investigated for L1 larvicidal activity, demonstrating 100% mortality at 1 µg/µL [84].

Finally, the species that presented poor larvicidal action for all tested extracts. *Aristolochia bracteata* Retz. (Aristolochiaceae) leaves methanolic extract was evaluated against L3 larvae (LC$_{50}$ 114.89 µg/mL), egg (100% non-hatchability at 240 ppm) and adult mosquito (100% repellency at 6 mg/cm$^2$) [81]. Similarly, *Caesalpinia pulcherrima* (L.) Sw. (Fabaceae) extracts were evaluated against larvae: benzene (LC$_{50}$ 136.37 µg/mL) and ethyl acetate (LC$_{50}$ 144.67 µg/mL), and 100% non-hatchability for benzene (375 ppm) and ethyl acetate (450 ppm). However, both extracts demonstrated 100% repellency at 5 mg/cm$^2$ [85].

In another study involving a methanol extract of *C. pulcherrima*, complete inhibition of egg hatching was reported at 300 ppm. The repellency was the same as the aforementioned study (5 mg/cm$^2$) [117]. *Coccinia indica* Wight & Arn. (Cucurbitaceae) presented similar insecticidal properties for different extracts, with a methanolic extract the most active in terms of ovicidal activity (zero hatchability at 200 ppm) and a hexanic extract having the more effective repellency (100% of repellency at 1 mg/cm$^2$). For 100% non-hatchability, the concentrations were between 200 ppm and 300 ppm and for 100% of repellency were between 1 and 5 mg/cm$^2$ [119].

The methanolic extract of *Eclipta alba* (L.) Hassk (Asteraceae) leaves was also the most active among the solvents of different polarities used to evaluate larvicidal and ovicidal activities of this plant. The LC$_{50}$ values against L3 larvae were between 127 and 165 µg/mL. Complete inhibition of egg hatching occurred at 300 ppm for the methanolic extract and 350 ppm for the other solvents [91].

The methanolic extract of *Mentha piperita* L. (Lamiaceae) and different extracts of *Cardiospermum halicacabum* L. ( Sapindaceae) showed repellent activity [118,120]. Essential oils and aqueous extracts of the red and pink flowers of *A. purpurata* were investigated for both larvicidal activity and oviposition effect. Similar to the essential oils, the extract of the pink flower was more active than the red, and both disrupted oviposition [67].

In general, organic extracts from different parts of *Parthenium hysterophorus* (Asteraceae), *Pithecellobium dulce* (Roxb.) Benth. (Fabaceae) and *Solanum xanthocarpum* Schrad. & J.C. Wendl. (Solanaceae) showed weak insecticidal action, requiring high concentrations to demonstrate some biological activity [111,114,121]. Other species that were inactive were *Helicteres velutina* K. Schum. (Malvaceae), *Monordica charantia* L. (Cucurbitaceae), *Ormosia arborea* Vell (Fabaceae), *Solanum variabile* Mart. (Solanaceae), *Spermacoce latifolia* Aubl. (Rubiaceae) and *Turnera ulmifolia* L. (Turneraeae) [88,95,106].

Several organic extracts have shown important insecticidal activities against the *Aedes* mosquito, including *E. transiliensis*, *E. tirucalli*, *H. japonicum*, *N. sarnisiensis*, *P. longum*, *P. ribesoides* and *P. sarmentosum*. Studies in this section show the potential of plant natural products as insecticides targeting different stages of the mosquito life cycle and how different formulation approaches, such as the incorporation of botanical extracts into silver and zinc nanoparticles, can increase the insecticidal
effects. Prominent examples include nanoformulations of *Z. gracilis*, *M. fragans* and *A. herba-herba* extracts. These data reinforce the large diversity of plants with toxic effect in different life stages of the *Aedes aegypti* mosquito. However, an important consideration for these materials is the type of extraction solvent employed, such as n-hexane, chloroform, benzene, given their toxicity to humans associated with harmful residues [122].

6. Secondary Metabolites

6.1. Terpenes

Terpenoids are a very promising target for the development of products of natural origin to be used in the control of the *Ae. aegypti* mosquito. These compounds were the most identified in the essential oils, extracts and purified fractions, generally having better results against the mosquito, especially in terms of larvicidal activity. Of the terpenes, monoterpenes are the most active and present great possibilities in bioinsecticide applications due to their low toxicity against mammals and non-target organisms [50].

This significant activity against the mosquito can be explained by the hydrophobicity of this class. Terpene toxicity against *Ae. aegypti* larvae may be associated with their nonpolar property as reported for other insects [123,124]. This property increases the ability of the compound to penetrate the hydrophobic larvae cuticle and renders them more toxic to the insect in comparison to polar compounds [123]. The chemical structures of the terpenes tested are shown in Figures 5–7.

Diterpene 7-oxo-8,11,13-cleistanthatrien-3-ol (28), isolated from the dichloromethane extract of *Vellozia gigantea* N.L. Menezes & Mello-Silva (Velloziaceae) adventitious roots, caused 100% larvae mortality at 416.06 µM [125]. The adulticidal activity of the diterpene phytol (29) was LC$_{50}$ 4.23 µM/mosquito [84].

The triterpenoids ursolic acid (30) and betulinic acid (22) showed larvicidal activity with LC$_{50}$ 245.24 µM and 310.83 µM, respectively. Their corresponding structures are illustrated in Figure 5. Bioassays of their chemical derivatives, with esterification of the hydroxyl group at the C-3 position, demonstrated less activity, suggesting that the hydroxyl group plays an important role in larvicidal activity [126].

![Figure 5. Diterpenes (A) and triterpenes (B) active against *Ae. aegypti*.](image-url)
Figure 6. Sesquiterpenes active against *Ae. aegypti*.

Figure 7. Monoterpenes active against *Ae. aegypti*.
The sesquiterpenes α-costic acid (31) and inuloxin A (32), both isolated from Inula viscosa (L.) Aiton (Asteraceae), demonstrated strong activity against L1 larvae. The concentration of each terpene required for 100% mortality was 4.27 µM and 4.03 µM, respectively [127]. Other sesquiterpene alkaloids with strong larvicidal activity (L3 and L4 instar) were 1-O-benzoyl-1-deacetyl-4-deoxyalatamine (33) (LC₅₀ 9.4 µM) and 1,2-O-dibenzoyl-1,2-deacetyl-4-deoxyalatamine (34) (LC₅₀ 2.3 µM). These sesquiterpenes with a β-dihydroagrofuran skeleton were isolated from M. oblongata stems [101].

β-caryophyllene (8) and caryophyllene oxide (35) demonstrated lower larvicidal activity, with LC₅₀ values of 127.23 and 135.24 µM, respectively [78], together with the sesquiterpene cinnamodial (36), isolated from C. fragrans (LC₅₀ 70 µM) [87]. Regarding adulticidal activity, sesquiterpenes isolated from C. fragrans—cinnamodial (36), cinnafra grin A (37) and cinnamosmolide (38)—showed strong activity with ED₅₀ 0.29, 2.85 and 12.79 nmol/mg mosquito, respectively [87].

Monoterpenes were the most evaluated for larvicidal activity with LC₅₀ values ranging from 88 to 540 µM. The terpene hydrocarbons: limonene (13) (LC₅₀ 88.16 µM); α-terpinene (39) (LC₅₀ 107.90 µM); α-phellandrene (40) (LC₅₀ 121.85 µM), and ρ-cymene (17) (LC₅₀ 143.05 µM) were the most active [61,72]. Terpinolene (41), γ-terpinene (42), β-myrcene (43) and sabinene (3) showed LC₅₀ 208.46 µM, 225.35 µM, 262.78 µM and 543.92 µM, respectively [61,71]. The oxygenated terpene hydrocarbons carvone (11) and cis-carveol (12) demonstrated activity with LC₅₀ of 155.62 µM and 218.88 µM, respectively [72].

A study of the larvicidal activity of α-pinene and β-pinene enantiomers reported the following LC₅₀ values: (-)-α-pinene (44) (263.52 µM) and (+)-α-pinene (45) (414.73 µM); (-)-α-pinene (46) (363.35 µM) and (+)-α-pinene (47) (484.26 µM). The (-) enantiomers displayed higher activity than (+), so these results showed that the type of enantiomer and even the racemic mixture could directly interfere with the activity [78].

The monoterpene limonene (13) was incorporated into a nanoemulsion to improve its water solubility and therefore increase its activity [68]. This compound deserves to be highlighted as it presented high oral LC₅₀ (>4000 mg/kg) and dermatological LC₅₀ (>5000 mg/kg) values for rodents. It is therefore considered safe and non-toxic to mammals [30].

6.2. Phenylpropanoids and Phenolic Derivatives

The chemical structures of the phenylpropanoids and esters discussed in this section are illustrated in Figure 8.

![Figure 8. Phenylpropanoids and phenolic derivatives active against Ae. aegypti.](image-url)
Among the phenylpropanoids and phenolic derivatives classes cinnamaldehyde (48) and cinnamyl acetate (49) can be highlighted as they presented interesting larvicidal activity (LC$_{50}$ 219.43 and 187.27 µM, respectively) [64]. It is important to note that cinnamaldehyde is present in commercial insect-fighting formulations such as Cinamite® and Valero®. This information suggests that these secondary metabolites have a high potential for use against Ae. aegypti due to their possible toxicological safety, given that they have been authorized as insecticides since 2001.

Important larvicidal properties were also reported for eugenol (15), a phenolic compound that presents some advantages such as its non-persistence in water and soil, together with its natural degradation in organic acids through the action of _Pseudomonas_, a soil-dwelling bacterium. Furthermore, it is 1500 times less toxic than pyrethrins and 15,000 times less toxic than azinphos-methyl, an organophosphate [50]. The LC$_{50}$ value for larvicidal activity was 200.97 µM [64]. The phenylpropanoid _trans_-anethole (7) also showed important action against _Ae. aegypti_ larvae (LC$_{50}$ 283.40 µM) [64].

Metabolites isolated from _Zingiber officinale_ Roscoe (Zingiberaceae) demonstrated strong larvicidal activity, presenting LC$_{50}$ values of 15.96 µM for 4-gingerol (50), 37.36 µM for 6-dehydrogingerdione (51) and 61.86 µM for 6-gingerol (52) [128]. The phenolic derivatives esters benzyl benzoate (53) and benzyl cinnamate (54)—demonstrated interesting activity as their 100% larvae mortality concentrations were 117.79 µM and 104.92 µM, respectively [45].

6.3. Alkaloids and Amides

The Piperaceae family has numerous compounds with promising activity against _Ae. aegypti_. The chemical structures of the aforementioned alkaloids and amides are illustrated in Figure 9.

![Figure 9. Alkaloids and amides active against Ae. aegypti.](image-url)

N-Isobutylamide alkaloids from _Piper_ species presented potent larvicidal and adulticidal activities. Secondary metabolites isolated from _P. nigrum_: pellitorine (55), guineensine (56), pipercide (57) and retrofractamide A (58) presented respective larvicidal LC$_{50}$ values of 4.12 µM, 2.32 µM, 0.28 µM and 0.12 µM [129]. Regarding the adulticidal activity, LC$_{50}$ values (µM/female mosquito) were 0.76, 4.43, 6.11 and 4.22, respectively [130]. Pipernonaline (59) isolated from the methanolic extract of _P. longum_, also showed potent larvicidal activity (LC$_{50}$ 0.73 µM) [127], while pipering (60) and pipwaqarine (61) isolated from _P. nigrum_ demonstrated LC$_{50}$ of 17.87 and 75.46 µM, respectively [131,132].

The analysis of the structure-activity relationship for the N-isobutylamide alkaloids 55–61, it is reasonable to hypothesise that the N-isobutylamine moiety is of crucial importance in terms of larvicidal activity, while the methylenedioxyphenyl moiety does not appear to be essential.
The mesembrine-type alkaloid sarriensinol (62) isolated from N. sarniensis exhibited strong larvicidal (LC\(_{50}\) 24.24 \(\mu\)M) and adulticidal (LC\(_{50}\) 13.88 \(\mu\)M/female mosquito) activities [104]. The crinine-type alkaloid crinsarine (63) only demonstrated strong adulticidal activity (LC\(_{50}\) 5.78 \(\mu\)M/female mosquito) [133]. N-hydroxyaristolactam I (64), an aristololactam derivative, also showed strong larvicidal activity (LC\(_{50}\) 11.45 \(\mu\)M) [130], whereas the pyrrolidine alkaloid (Z)-3-(4-hydroxybenzylidene)-4-(4-hydroxyphenyl)-1-methylpyrroldin-2-one (65) demonstrated weak activity (LC\(_{50}\) 785.86 \(\mu\)M) [134,135].

6.4. Thiophenes and Acids

Thiophene and fatty acid chemical structures are illustrated in Figure 10.

![Figure 10. Fatty acids and thiophene derivatives active against Ae. aegypti.](image)

Nine thiophenes, with different numbers of thiophene rings, isolated from E. transiliensis exhibited strong larvicidal activity and a positive correlation was reported between the number of thiophene rings and larvicidal activity, with thiophene derivatives composed of more rings demonstrating more activity [90].

The terthiophene 2,2′: 5′,2″-terthiophene (66) was the most active (LC\(_{50}\) 0.65 \(\mu\)M). The activity (LC\(_{50}\)) of bithiophenes was: 4-(2,2′-bithiophen-5-yl)but-3-yne-1,2-diyldiacetate (67) (12.54 \(\mu\)M); 4-(2,2′-bithiophen-5-yl)-2-hydroxybut-3-yn-1-yl acetate (68) (25.31 \(\mu\)M) and 4-(2,2′-bithiophen-5-yl)but-3-yn-1,2-diol (69) (39.19 \(\mu\)M). Lower larvicidal activity was observed for monothiophenes: 2-chloro-4-[5-(penta-1,3-diyn-1-yl)]thiophen-2-yl]but-3-yn-1-yl acetate (70) (49.56 \(\mu\)M); 4-[5-(penta-1,3-diyn-1-yl)]thiophen-2-yl]but-3-yn-1,2-diyl diacetate (71) (56.02 \(\mu\)M); 4-[5-(penta-1,3-diyn-1-yl)]thiophen-2-yl]but-3-yn-1,2-diyl diacetate (72) (56.68 \(\mu\)M); 2-hydroxy-4-[5-(penta-1,3-diyn-1-yl)]thiophen-2-yl]but-3-yn-1-yl acetate (73) (66.64 \(\mu\)M) and 1-hydroxy-4-[5-(penta-1,3-diyn-1-yl)]thiophen-2-yl]but-3-yn-2-yl acetate (74) (71.74 \(\mu\)M) [90].
Another furanochromone isolated from *A. visnaga* and *G. ternifolia* were active against L2 larvae. The LC₅₀ values were 108.09 µM, 85.37 µM and 102.08 µM, respectively [94].

### 6.5. Flavonoids

The corresponding chemical structures are shown in Figure 11. Quercetin-4′,7-O-dimethyl ether (78), naringenin-7-O-methyl ether (79) and kaempferol-7-O-methyl ether (80) flavonoids isolated from *G. ternifolia* were active against L2 larvae. The LC₅₀ values were 108.09 µM, 85.37 µM and 102.08 µM, respectively [94].

![Figure 11. Flavonoids active against Ae. aegypti.](image)

### 6.6. Neolignans

Figure 12 details the neolignan chemical structures.

![Figure 12. Neolignans active against Ae. aegypti.](image)

Eupomatenoid-6 (81), a neolignan isolated from *Piper solmsianum* C. DC. (Piperaceae), demonstrated strong larvicidal acitivity (LC₅₀ 19.33 µM) with probably low toxicity to mammals (IC₅₀ 39.30 µM for human fibroblast cells, MRC5, with an estimated LD₅₀ of 42.26 mmol/kg) [138]. Grandisin (82) presented larvicidal activity (LC₅₀ 346.82 µM). Histological analysis revealed that this neolignan damages the anterior-middle midgut of the larvae [139].

### 6.7. Furanochromones and Furanocoumarin

The chemical structures of the coumarins are illustrated in Figure 13.

Khellin (83), a natural furanochromone isolated from *Ammi visnaga* (L.) Lam. (Umbelliferae), caused L3 mortality (LC₅₀ 192.1 µM) [140]. In another study, 83 demonstrated 100% larval mortality at 3.84 µM and 75% adult mortality at 19.21 µM/mosquito for permethrin-susceptible strains [141]. Another furanochromone isolated from *A. visnaga*, visnagin (84) presented 93% mortality at 4.34 µM, together with moderate adulticidal activity (65% mortality at 21.72 µM/mosquito). In addition, this study investigated 2 furanocoumarins isolated from *Ruta graveolens* L. Royle (Rutaceae): 5-methoxypsoralen (5-MOP) (85) and 8-methoxypsoralen (8-MOP) (86), which showed moderate adulticidal activity (55%...
mortality at 23.13 µM/mosquito and 67.5% mortality at 23.13 µM/mosquito, respectively). Compound 86 presented weak activity against L3 (53.3% mortality at 4.63 µM) while 85 was inactive [141].

Figure 13. Furanochromones and furanocoumarins active against Ae. aegypti.

6.8. Other Secondary Metabolites

The chemical structures of the compounds referenced in this section are illustrated in Figure 14.

Several other classes of plant natural products have also been investigated regarding their insecticidal activities. Naphthoquinone 2-methoxy-1,4-naphthoquinone (87) isolated from Impatiens glandulifera (Balsaminaceae) showed extremely potent larvicidal acitivity (LC50 0.45 µM) and moderate adulticidal activity (40% mortality at 26.6 µM) [127]. Nilocetin (88), a protolimonoid isolated from L. acidissima, also demonstrated very strong larvicidal (LC50 0.96 µM) and pupicidal (LC50 1.36 µM) activity which was higher than temephos, a well-documented chemical insecticide. The triterpenoid also caused 83% egg mortality at 4.38 µM [99]. Already a study evaluating volatile plant metabolites capable of eliciting an Ae. aegypti behavioral response reported that acetophenone (89) attracted adult mosquitoes whereas 1-octanol (90) acted as a repellent (flight aversive response) [142].
7. Mechanisms of Action

The mechanisms of action for the *Ae. aegypti* control relate more to the use of conventional chemical insecticides. Table 5 summarizes the mechanisms of action data of the botanical samples discussed in this section. *Ae. aegypti* control relies primarily on the use of conventional chemical insecticides which target different critical sites in the mosquito life cycle. Organophosphates and carbamates, for example, target acetylcholinesterase enzyme inhibition. Pyrethrroids and some organochlorines target sodium channels. Cyclodiienes and polychloroterpenes target gamma-aminobutyric acid (GABA) receptors [34].

Other mechanisms of alternative insecticides authorized by regulatory agencies vary in terms of their action. For example, a biological approach employs the use of entomopathogenic bacteria (*Bacillus thuringiensis israelensis* and *Bacillus sphaericus*), which act via the toxic action of their spores damaging the intestinal epithelium of larvae. Insect growth regulators (IGR) differ in that they inhibit insect chitin synthesis, and therefore disrupt the molting process, while juvenile hormone analogs (JHA) act by interfering with the insect’s endocrine system [138].

Further studies are required in order to completely understand the various toxic action mechanisms of botanical insecticides. However, a number of mechanisms have been proposed and proven. The majority of mechanism of action studies have focused on the larval stage, particularly feeding and/or contact. In the case of ingestion, the action is usually through digestive toxicity whereas contact may involve enzymatic inhibition, endocrine disruption (acting especially during the molting process), toxicity to the nervous system and other mechanisms depending on the target site [143].

The rapid toxic action of essential oils against the insect indicates a possible neurotoxic mode of action [144]. Phytochemicals may act in cholinergic, GABA, mitochondrial and octopaminergic systems [145]. A study of five volatile compounds commonly found in plant essential oils—eugenol, geraniol, coumarin, eucalyptol and carvacrol—investigated docking against octopamine and acetylcholinesterase receptors in *Ae. aegypti* and *Homo sapiens* protein models. All compounds were found to dock in both protein models, with some more selectivity for insect proteins [146].

Effects on the larval nervous system were observed after treatment with *Piper* species extracts. Tremor, convulsion, excitement, followed by paralysis and death were verified after exposure of larvae to *P. longum*, *P. ribesoides* and *P. sarmentosum* extracts. In addition, the larvae showed morphological changes in the anal papillae [109].

Essential oils of *I. verum*, *P. dioica* and *M. fragrans* inhibited acetylcholinesterase causing acetylcholine accumulation in the synapses, with the membrane in a constant state of excitement, culminating in ataxia, lack of neuromuscular coordination and eventual death [54]. The neurotoxic effect was also observed for a nanoemulsion with *P. emarginatus* essential oil. It probably causes reversible inhibition of acetylcholinesterase and consequently larval death [66].

*D. brasiliensis* extracts caused external morphological alterations in the larvae, resulting in interference in the molting process. The authors also reported digestive toxicity and morphological changes in the anal papillae and respiratory siphon of the larvae which interfered with swimming and oxygen flow [89]. Similarly, nilocetin (88) (Figure 14) induced morphological deformations together with molting symptoms and growth disruption in all mosquito life cycle stages. These compounds also totally ruptured the peritrophic membrane [99].

A *Lonchocarpus urucu* extract caused disruption in the peritrophic matrix, a medium intestine lining composed of chitin and proteins, whose functions are to protect against abrasion caused by food and micro-organisms, among others such as decreasing the excretion of digestive enzymes through their recycling. In addition, this extract caused extensive damage to the midgut epithelium (Table 5) [100].
Table 5. Mechanisms of action of botanicals against the *Ae. aegypti* mosquito.

| Target Site           | Mechanism of Action                                                                 | Compound                  | Plant Species                                         | Reference |
|-----------------------|-------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------------|-----------|
| Nervous system        | Inhibition of acetylcholinesterase (AChE)                                            | Essential oil             | *Illicium verum, Pimenta dioica and* Myristica fragrans | [54]      |
|                       |                                                                                     | Nanoemulsion with essential oil | *Pterodon emarginatus*                                 | [66]      |
|                       |                                                                                     | Ethanolic extract         | *Piper longum, Piper ribesoides and Piper sarmentosum* | [109]     |
| Gut trypsin           | Inhibition of trypsin and consequent decreased absorption of nutrients and essential amino acids | Aqueous extract           | *Moringa oleifera*                                    | [147]     |
|                       |                                                                                     | Essential oil             | *Croton rhamnifoloides*                                | [70]      |
|                       |                                                                                     | Methanol extracts         | *Derris (Lonchocarpus) urucu*                          | [100]     |
|                       |                                                                                     | Nilocetin                 | *Limonia acalissima*                                   | [99]      |
|                       |                                                                                     | Methanol extracts         | *Derris (Lonchocarpus) urucu*                          | [100]     |
|                       |                                                                                     | Pellitorine               | *Asarum heterotropoides*                               | [148]     |
|                       |                                                                                     | Grandisin                 | *Piper solnsium*                                       | [139]     |
| Peritrophic matrix    | Change in internal morphology and consequent insect protection dysfunction           | Methanol extracts         | *Asarum heterotropoides*                               | [148]     |
|                       |                                                                                     | Nilocetin                 | *Limonia acalissima*                                   | [99]      |
| Midgut epithelium     | Tissue destruction and cell disorganization                                           | Pellitorine               | *Asarum heterotropoides*                               | [148]     |
|                       |                                                                                     | Grandisin                 | *Piper solnsium*                                       | [139]     |
|                       |                                                                                     | Crude extracts            | *Dalbergia brasiliensis*                               | [89]      |
|                       |                                                                                     | Ethanolic extract         | *Piper longum, Piper ribesoides and Piper sarmentosum* | [109]     |
| Anal papillae         | Morphological changes, interference with the larva swim                               | Crude extracts            | *Dalbergia brasiliensis*                               | [89]      |
|                       |                                                                                     | Nanoemulsion with limonene| *Baccharis reticularia*                                 | [68]      |
|                       |                                                                                     | Pellitorine               | *Asarum heterotropoides*                               | [148]     |
|                       |                                                                                     | Crude extracts            | *Dalbergia brasiliensis*                               | [89]      |
| Respiratory siphon    | Morphological changes, interference with the oxygen flow                              | Nanoemulsion with limonene| *Asarum heterotropoides*                               | [148]     |
| Anal gills            | Comprehensive damage; debris in hemolymph                                            | Pellitorine               | *Asarum heterotropoides*                               | [148]     |
| Thorax and exoskeleton| Changes in external morphology, interfering with the molting process                  | Pellitorine               | *Limonia acidissima*                                   | [99]      |
|                       |                                                                                     | Nilocetin                 | *Baccharis reticularia*                                 | [68]      |
| Digestive system      | Digestive toxicity                                                                   | Nanoemulsion with limonene| *Dalbergia brasiliensis*                               | [89]      |
|                       |                                                                                     | Crude extracts            | *Dalbergia brasiliensis*                               | [89]      |
Pellitorine (55), an isobutylamide alkaloid, whose structure is illustrated in Figure 9, promoted histological changes in the thorax, midgut and anal gills. These toxic effects probably occur as a result of compound action on the larval osmoregulation system [148]. Already a nanoemulsion with limonene (13) (Figure 7) promoted morphological alterations to the head, siphon, abdomen cuticles and thorax, promoting larvae fragility and low mobility [68].

*C. rhamnifolioides* essential oil induced toxicity in the larvae by trypsin-like activity. Trypsin is a serine protease that widely occurs in the gut of insects. A decrease in its activity may result in poor nutrient absorption and non-availability of essential aminoacids, causing insect death [72]. A *Moringa oleifera* (Moringaceae) extract also caused larval toxicity by inhibiting trypsin in the gut [147]. After treatment with grandisin (82) (Figure 12), larvae presented intense tissue destruction and cell disorganization in the anterior midgut [139].

### 8. Limitations and/or Expectations of Plant Natural Product Insecticide Applications

As demonstrated in this review, natural products of botanical origin are promising for control of the *Ae. aegypti* mosquito, although there remain several limitations and challenges to overcome for their application as insecticidal products. From 1998 until early 2011, the number of patents of essential oil-containing mosquito repellent inventions has almost doubled every 4 years [149], but the number of new products does not reflect this. There are several possible reasons for this disparity, such as: (i) the onerous regulatory processes involved in the registration of a pesticide product; (ii) the quantity of raw material biomass required to obtain sufficient extract and/or its isolated active compound, and (iii) most of the research is conducted at the laboratory scale often without field evaluation to confirm the product application [13,47,150].

The complex process of registering an insecticide discourages companies from investing in new products, especially in some places such as Brazil and the European Union. There are numerous criteria, including provision of non-target toxicology and environmental destination data, extensive data to guarantee plant stability and extract standardization, together with physico-chemical and microbiological procedures establishing quality control of the raw material and final product [47,48].

The low availability of raw materials due to limited yields and cultivation usually makes botanical insecticides more expensive than chemicals. The study of bioactive compound synthesis through biotechnology, such as tissue culture in bioreactors, constitutes an alternative to this limitation [150,151]. In moving from laboratory to industrial scale, a number of different factors must be considered: botanical material, analysis technique, formulations, toxicological tests, mechanisms of action, among others.

Considering the botanical material, it is essential to correctly identify the botanical species and determine the chemical composition of the extract (standardization) [13,50]. Chemical composition may vary depending on numerous factors, such as crop period, seasonality, phenological stage, temperature, humidity, luminosity, altitude, pluviometry, ultraviolet radiation, soil and nutrient conditions, geographical locations, collection method, drying and the part of the plant used, among others, and consequently impact insecticidal activity [152–155].

Regarding larvicidal analysis techniques, important considerations are: (i) larval phase, (ii) analysis time, and (iii) the use of positive and negative controls. In different studies, the younger the larval stage, the more susceptible it is to toxic effects, as reported for *Ficus benghalensis, Heracleum rigens, Myristica fragans* and *Solanum xanthocarpum* (Table 3) [53,93,96,114]. This characteristic may relate to the reduced feeding of larvae in the late L4 instar. If the toxic effect of the insecticide is ingestion-dependent, the effect may be less pronounced the closer the larva is to the pupa stage of metamorphosis [156]. Although most studies use 24 h as the contact time to express the mortality result, it is important to note that some materials may have delayed activity, actually causing larvae death after 48, 72 or even 96 h. Thus, during product development, it is necessary to assess the toxic effect at different time intervals. Finally, the use of negative and positive controls is essential to ensure results reliability, although a number of studies did not report this data [157]. Therefore, test non-uniformity makes it
difficult to compare the results of different studies. This constitutes another obstacle to overcome for the development of plant natural product insecticides [158].

Understanding the mechanism of action is fundamental in using a material as an insecticidal product. Knowledge of the mechanism of action makes it possible to understand which non-target organisms could be harmed by the use of such products [145,159]. In addition, this information facilitates prospecting other possibly more active materials using biotechnology tools and in silico models [160–162]. However, in general it is not easy to understand the mechanisms of action of plant natural products. Normally there are multiple modes of action pertaining to the complex composition of the materials [30,49,145], that usually occur in different target sites, as described for *Piper* spp, *Derris* (*Lonchocarpus*) *urucu*, *Asarum heterotropoides* and *Dalbergia brasiliensis* (Table 5) [89,100,109,148].

During the development stage, it is essential to evaluate toxicity in non-target organisms for promising insecticides using suitable models, such as the fish embryo acute toxicity (FET) test [163]. This model has been proposed to determine the acute or lethal toxicity of materials in the embryonic stages of zebrafish (*Danio rerio*) and for environmental assessments [163,164]. In addition, it is important to consider other aquatic and terrestrial organisms according to the intended application location, such as fish, amphibians, bees, birds and mammals [159]. Considering that natural product insecticides have natural degradation mechanisms, they possibly present advantages in comparison with insecticides of synthetic origin [26,30,50].

In general, raw materials (essential oils, extracts and isolated compounds) from plant natural products are poorly soluble in water and do not persist in the environment, which complicates the application and reduces the effectiveness of the desired action [26,51,165]. Therefore, the use of pharmaceutical technology is of fundamental importance in the development of formulations. Among the techniques used, nanotechnology, encapsulation and use of hydrophobic matrices with an extended and controlled release system should be highlighted as they can prolong the residual effect of formulations [51,149,165–167] due to controlled release. Formulation development of natural products also poses a challenge for the application of these materials but it is imperative to improve both efficiency and cost-effectiveness [150,165]. Investing in botanical natural product formulations is an important advance in increasing the availability of commercial eco-friendly insecticides for *Ae. aegypti* control.

### 9. Conclusions

Considering the several stages of the insect development, the larvicidal test is the most evaluated bioassay in the search for insecticides to control *Ae. aegypti* for a number of reasons: (i) the larval phase is the longest in the immature stage; (ii) larvae are generally more sensitive to the toxic effects of compounds, and (iii) larvae breeding sites are localized and usually accessible. The search for ovicidal action is complex, especially due to its composition that hinders the toxic action of compounds. For the adult phase, there are compounds that cause toxicity by contact as well as those with repellent action.

Some very common edible botanical species such as *Petroselinum crispum*, *Foeniculum vulgare*, *Curcuma longa*, *Mentha spicata*, *Ocimum gratissimum* and *Rosmarinus officinalis* are highlighted, especially in the larval phase of *Ae. aegypti*, due to their possible low toxicity to non-target organisms. However, other non-edible species have shown strong larvicidal extract activity, among them *Echinops transiliensis*, *Piper* spp, *Hypericum japonicum* and *Nerine sarniensis*.

Essential oils provide a promising source for insecticidal applications due to their important insecticidal activities and possible toxicological safety for mammals and the environment. Moreover, they generally possess high oral and dermal LC50 values for these animals and are more readily degraded by natural ecosystem mechanisms.

Among the secondary metabolites, terpenes, especially monoterpenes, and phenylpropanoids are highlighted for larvicidal activity. These compounds are present in large quantities in essential oils. In addition, thiophenes, amides and alkaloids demonstrate high larvicidal and adulticidal activity.
Regarding the mechanisms of action, botanical natural products extracts, and pure compounds have displayed activities that include altering insect morphogenesis and therefore impairing the moultng process, respiration, feeding, and self-defense, among others. In addition, they altered biochemical processes and the nervous system.

Despite the limitations and obstacles to overcome, plant natural products are a suitable alternative source of eco-friendly botanical insecticides to control the *Ae. aegypti* mosquito, popularly known as dengue mosquito. Ever increasing mosquito resistance to conventional chemical insecticides warrants alternative products, which are safer for the environment and pose less risk to human health.

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