A Review of the Bioactivity of Plant Products Against *Aedes aegypti* (Diptera: Culicidae)[1]

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Abstract The mosquito *Aedes aegypti* L. (Diptera: Culicidae) is a disease vector for several pathogens that affect human health worldwide. Therefore, there is a need to produce synthetic chemicals that can effectively control mosquitoes; however, these chemicals can also cause a range of environmental and health problems. In the present review, we compiled all available information from the literature between 2005 and 2018 on plant products that have been used to control *A. aegypti* and tabulated their modes of action. This review classifies these plant-based products according to their bioactivities (toxicity, repellency, feeding deterrence, and oviposition deterrence) and provides new insights, findings, and patterns of their application. Plants contain a wide spectrum of chemical compounds that can effectively control mosquito populations; therefore, they should be developed to control diseases transmitted by mosquitoes. Plant products are mostly safe for human, animal, and environmental health. Moreover, because of the diversity and low use of plant-derived compounds as insect control agents, mosquitoes have not acquired resistance to them. The present review indicated that the bioactivities of many plant compounds can effectively control *A. aegypti* in laboratory conditions, and the comprehensive cataloging and classification of natural plant product bioactivities in this review will facilitate the search for new applications of these substances in insect pest control strategies.

Key Words mosquito vectors, toxicity, repellents, antifeedants, oviposition deterrents

The mosquito *Aedes aegypti* (L.) transmits viruses that cause many diseases, such as yellow fever, chikungunya, dengue, and Zika viruses, that threaten human health (Githeko et al. 2000, Hennessey et al. 2016, Gregory et al. 2017). *Aedes aegypti* is 4–7 mm in length, has black coloration with white dots on its legs, and has white lines on its thorax (Carpenter and LaCasse 1955). After mating, the females bite humans, mammals, and birds to obtain the blood needed to meet its protein requirements for oviposition. Female *A. aegypti* can bite at any time of the day, but biting frequency tends to increase at sunset (Carpenter and LaCasse 1955). Female mosquitoes lay eggs five times in their lifespan; they produce approximately 100–200 eggs after a full blood meal. The lifespan of *A. aegypti* can range from 2 weeks to 1 mo, and its eggs are laid individually in stagnant water around houses, in containers, and in tree holes. When the eggs hatch, the larvae survive for approximately 4 d on water-based food sources, such as algae, and then fast for 2 d

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during pupation, after which the adult mosquitoes emerge (Zettel and Kaufman 2012).

Control of mosquito populations is one of the most effective ways to reduce the spread of viral diseases transmitted mainly by mosquitoes. Chemicals can control disease vector mosquitoes, but they are associated with several disadvantages. Therefore, researchers have focused on assessing the efficacy of plant-based pesticides and identifying their active ingredients to produce safe and effective pest control products. More than 2,000 plant species are known to produce chemicals with medicinal and insecticidal properties that could have a potential role in pest control programs (Ghosh et al. 2012). Previous reviews focused mainly on the bioactivity of plant extracts and essential oils in laboratory formulations, and few of these are actually used for mosquito control in practice. The present review aimed to compile information published between 2005 and 2018 on plant products that could be used to control *A. aegypti*. The bioactivities of these compounds are classified as toxic, repellent, antifeeding, or oviposition deterrent activities in mosquitos.

Mosquito Control Using Plant Products

Plants contain chemicals that are effective against certain target insects, which could be used to control mosquitoes and reduce their spread. Plant products are generally considered less harmful for humans and the environment than synthetic chemicals (Bokhari et al. 2014, Gbolade et al. 2000, Shivakumar et al. 2013, Nasir et al. 2015); therefore, plant products are regarded as ideal substitutes for conventional chemical pesticides (Ngadino and Sudjarwo 2017). Plant products are also abundant sources of effective and biodegradable biological compounds, and insect resistance to these products is limited; however, in the development of alternative pest control substances, the risk of insect tolerance merits serious consideration and further investigation.

Numerous studies have shown that plants and their products can be used to control all life stages of mosquitoes (Table 1) and may exhibit repellent, toxic, antifeeding, or antioviposition effects. Most of the plant products tabulated in Table 1 are indicated as toxic and have various types of bioactivity. The present review catalogs these products and classifies their bioactivities based on their effectiveness.

Toxic Effect of Plant Products on Mosquitoes

Pest control involves the use of materials to kill or reduce the number of the target insects. Such materials are classified according to their modes of action (e.g. acetylcholinesterase inhibitors or antagonists, sodium channel blockers, and nicotinic acetylcholine receptor agonists) and their methods of administration to insects (e.g. contact, ingestion, and fumigation). Toxicity can be quantified by calculating the concentration-mortality or dose-mortality responses to the compound.

Plants contain chemical compounds, such as flavonoids, tannins, saponins, alkaloids, and volatile oils, that are known for their toxic effects against various types of insects (Ngadino and Sudjarwo 2017). Moreover, plant products have various modes of action against target insects. The most prominent of these modes is acetylcholinesterase inhibition or octopamine antireception, both of which impair insect nervous system function, resembling the effects of certain chemical pesticides. Studies have shown that volatile and monoturbo oils can cause insect death by inhibiting acetylcholinesterase (Sendi and Ebadollahi 2013). In addition, many plant oils can harm insect nervous systems by affecting ketamine receptors (Sendi and Ebadollahi 2013). Certain plant-derived compounds mimic acetylcholine in mammalian neuromuscular centers and cause spasms and twitches to occur in rapid succession, which lead to the death of target insects (Ware 2000). Furthermore, certain plant products affect sensory nerves of the superficial nervous system in insects. However, there are also plant products that do not affect the insect nervous system. For example, limonene extracted from citrus peel does not affect cholinesterase (Ware 2000). Previous studies have shown that certain plant compounds, such as azadirachtin extracted from the seeds of *Azadirachta indica* A. Juss, exhibit pesticidal activities (Ware 2000) by mimicking growth regulators, influencing maturation and senescence, and causing death. Moreover, seed and leaf extracts of *Argemone mexicana* L. differ in efficacy against mosquitoes (Sakthivadivel and Daniel 2008). Modes of action can, thus, vary even between extracts from the same plant.

Plant Products Used as Mosquito Repellents

Natural or chemically produced repellents are nontoxic, but their appearance, flavor, and odor can change insect behavior. Mosquitoes are naturally attracted to human body temperature, respiration, and carbon dioxide exhalation (Tauxe et al. 2013); however, repellents can prevent mosquitoes from landing on exposed skin. The effectiveness of repellent products is rated in several ways and a common method involves the use of an olfactometer and volunteers. Mosquito bites with and without repellent application are counted and repellent effectiveness is calculated using the Weaving and Sylvester formula (Weaving and Sylvester 1967): repellency (%) $= 100 -$ number of bites on control arm/number of bites on treated arm $\times$ 100. In most studies, plant product repellency is calculated using the formula from Sharma and Ansari (1994) and Yap et al. (1998): repellency (%) $= C - T/C \times 100$ where $C =$ number of bites in the control and $T =$ number of bites in the treated group.

Currently available repellents include allethrin, *N,N*-diethyl-*m*-toluamide, dimethyl phthalate, and *N,N*-diethyl mandelic acid amide, which repel mosquitoes effectively but are reported as unsafe for common use (Roland et al. 1985, Zadikoff 1979). Therefore, researchers are attempting to find alternative repellents from natural plant sources with efficacy comparable to those of conventional products but without any harmful effects to users. The ideal products should be nontoxic, environmentally friendly, unlikely to damage sensitive skin, and safe for children from the age of three months (Patel et al. 2012). However, these products may be costly and may require frequent or repeated application because they evaporate quickly. Moreover, certain products may cause allergic reactions when applied directly to the skin (Patel et al. 2012). The efficacy of repellents can be improved by changing their chemical structures to increase their stability and their ability to remain in contact with the skin for longer periods of time (Maji et al. 2007).

Table 1. Bioactivity of plant products against *Aedes aegypti*, arranged by publication year.

Reference	Bioactivity Type			Affected Stage	Descriptors as Reported in the References	Plant Species
	Antifeedant	Toxicant	Repellent			
Ansari et al. 2005	NA	*	NA	Larvae	Industrially extracted and commercially supplied oils	*Pinus longifolia*
Trongtokit et al. 2005	NA	NA	*	Adult	Undiluted oils	*Cymbopogon nardus* *Pogostemon cablin* *Syzygium aromaticum* *Zanthoxylum limonella*
Kamaraj et al. 2008	NA	*	NA	Larvae	Extract (leaves)	*Ocimum canum* *Ocimum sanctum* *Rhinacanthus nasutus*
Kumar et al. 2011	NA	*	+	Adult and larvae	Essential oils (leaves)	*Mentha piperita*
Phasomkusolsil and Soonwera 2011	NA	NA	*	Adults	Essential oils	*Cymbopogon citrates* *Cymbopogon nardus* *Syzygium aromaticum* *Ocimum basilicum*
Sritabutra et al. 2011	*	NA	*	Adults	Essential oils	*Cybopogon citrates* *Eucalyptus globulus* *Ocimum basilicum*
Manimaran et al. 2012	NA	*	NA	Larvae	Oils (leaves)	*Mentha piperita*

Table 1. Continued.

Reference	Bioactivity Type			Affected Stage	Descriptors as Reported in the References	Plant Species
	Antifeedant	Toxicant	Repellent			
Shivakumar et al. 2013	NA	*	NA	Larvae	Extract (leaves)	*Blepharis maderaspatensis* *Elaeagnus indica* *Maaesa indica* *Phyllanthus wightianus* *Memecylon edule*
Tennyson et al. 2013	NA	*	NA	Larvae	Oils	*Citrus sinensis* *Cymbopogon martini* *Myristica fragrans*
Fernandez et al. 2014	NA	*	NA	Larvae	Essential oils	*Tetradenia riparia*
Kiplang'at and Mwangi 2014	NA	NA	*	Adult	Extract (leaves)	*Chrysanthemum cinerariaefolium* *Azadirachta indica*
Meenakshi and Jayaprakash 2014	NA	*	NA	Larvae	Extract (leaves)	*Rhizophora mucronata*
Pierre et al. 2014	NA	*	NA	Larvae	Extract (leaves)	*Callistemon rigidus*
Queen et al. 2014	NA	NA	*	Adult	Dried powdered leaves	*Pongamia glabra* *Calotropis gigantea* *Vinca rosea* *Chrysanthemum indicum* *Adhatoda vasica*

Table 1. Continued.

Reference	Bioactivity Type			Affected Stage	Descriptors as Reported in the References	Plant Species
	Antifeedant	Toxicant	Repellent			
Rocha et al. 2015	NA	*	NA	Larvae	Essential oils	*Foeniculum vulgare*
Aguiar et al. 2015	NA	*	*	Egg, larvae, pupae, and adult	Essential oils	*Siparuna guianensis*
Ananth and Mani 2015	NA	*	*	Adult and larvae	Extract (leaves)	*Acalypha ornata*
Pérez López et al. 2015	NA	*	NA	Larvae	Essential oils	*Zanthoxylum fagara* *Ruta chalepensis* *Thymus vulgaris*
Nasir et al. 2015	NA	*	NA	Larvae and pupae	Essential oils (leaves-branches) Rhizome of ginger	*Eucalyptus globules* *Mentha piperita* *Zingiber officinale* Rosc.
Sathantriphop et al. 2015	NA	*	*	Adult	Essential oils	*Cymbopogon nardus* *Ocimum americanum* *Nepeta cataria* *Vetiveria zizanioides*
Soonwera 2015a	*	*	NA	Adult	Essential oils	*Citrus aurantium* *Citrus aurantifolia* *Citrus hystix* *Citrus maxima* *Citrus medica* *Citrus reticulate*

Table 1. Continued.

Reference	Bioactivity Type			Affected Stage	Descriptors as Reported in the References	Plant Species
	Antifeedant	Toxicant	Repellent			
Ali et al. 2015	*	*	*	Adult and larvae	Essential oils (flower-leaf-stem)	*Echinophora lamondiana*
Da Silva, Milet-Pinheiro, et al. 2015	NA	*	NA	Larvae	Essential oils (leaves)	*Eugenia brejoensis*
Arivoli et al. 2016	NA	*	NA	Larvae	Ethyl acetate whole-plant extract	*Sphaeranthus indicus*
Auysawasdi et al. 2016	NA	NA	*	Adult	Essential oils	*Curcuma longa* *Eucalyptus globulus* *Citrus aurantium*
Cantrell et al. 2016	NA	NA	*	Adult	Essential oils	*Hierochloë odorata*
Da Silva Carvalho et al. 2016	NA	*	NA	Adult and larvae	Essential oils (leaves)	*Croton tetradenius*
Da Silva et al. 2016	NA	*	NA	Adult	Essential oils (leaves)	*Piper corcovadensis*
Govindarajan et al. 2016	NA	*	*	Larvae	Essential oils	*Zingiber nimmonii*
Misni et al. 2016	NA	NA	*	Adult	Essential oil (leaves, fruit peel, rhizome)	*Citrus aurantifolia* *Citrus grandis* *Alpinia galanga*
Oliveira et al. 2016	NA	*	NA	Larvae	Oils (fruits)	*Pterodon emarginatus*

Table 1. Continued.

Reference	Bioactivity Type: Antifeedant	Bioactivity Type: Toxicant	Bioactivity Type: Repellent	Affected Stage	Descriptors as Reported in the References	Plant Species
Intirach et al. 2016	NA	*	NA	Adult and larvae	Essential oils and ethanolic extracts	*Petroselinum crispum*
Santana et al. 2016	NA	*	NA	Larvae	Essential oils	11 species of *Piper* from Panama
Uniyal et al. 2016	NA	NA	*	Adult	Essential oils (fruit)	*Litsea cubeba*
Alvarez Costa et al. 2017	NA	*	*	Larvae	Essential oils	*Eucalyptus nitens*
Amir et al. 2017	NA	*	NA	Larvae	Extract (leaves)	*Parthenium hysterophorus*
Benelli et al. 2017	NA	*	NA	Larvae	Essential oils	*Blumea eriantha*
Botas et al. 2017	NA	*	NA	Larvae	Essential oils	*Baccharis reticularia*
Castillo et al. 2017	NA	*	*	Adult and pupae	Essential oils	*Lippia alba* *Lippia origanoides* *Eucalyptus citriodora* *Cymbopogon citratus* *Cymbopogon flexuosus* *Citrus sinensis* *Cananga odorata* *Swinglea glutinosa* *Tagetes lucida*

Table 1. Continued.

Reference	Bioactivity Type			Affected Stage	Descriptors as Reported in the References	Plant Species
	Antifeedant	Toxicant	Repellent			
Cruz et al. 2017	NA	*	NA	Adult and larvae	Essential oils	*Croton argyrophyllus*
Nentwig et al. 2017	NA	NA	*	Adult	(Seeds oil)	*Syzygium aromaticum*
Ngadino and Sudjarwo 2017	NA	*	NA	Larvae	Extract	*Pinus merkusii*
Porto et al. 2017	NA	*	NA	Larvae	Extract (leaves)	*Ormosea arborea* *Turnera ulmifolia* *Piper hispidum* *Spermacoce latifolia*
Ríos et al. 2017	NA	*	NA	Larvae	Essential oils	*Thymus vulgaris* *Salvia officinalis* *Lippia origanoides* *Eucalyptus globulus* *Cymbopogon nardus* *C. martinii* *L. alba* *Pelargonium graveolens* *Turnera diffusa* *Swinglea glutinosa*
Thanigaivel et al. 2017	NA	*	*	Adult	Essential oils	*Justicia adhatoda* L.

Table 1. Continued.

Reference	Bioactivity Type			Affected Stage	Descriptors as Reported in the References	Plant Species
	Antifeedant	Toxicant	Repellent			
Vivekanandhan et al. 2017	NA	*	NA	Adult, larvae, and pupae	Extract (crude leaves)	*Acanthospermum hispidum*
Zhai et al. 2017	NA	NA	*	Adult	Essential oils	*Eleutherococcus senticosus*
Govindarajan et al. 2018	NA	*	NA	Larvae	Essential oils	*Galinsoga parviflora*

*, bioactivity found; NA, bioactivity not tested.

The efficacy of plant products as mosquito repellent depends on several factors, such as the type of repellent material, application method, environmental factors, exposure duration, and insect pest sensitivity (Maia and Moore 2011). Plant-based repellents can be included in aerosols, wet wipes, creams, or moisturizers. The quantity of repellent used will vary with the type of materials it is suspended in. Plant volatile oils could replace synthetic insect repellents because the former consist of monoterpenes, such as cineole, eugenol, terpinolene, camphor, citronella, limonene, citronellol, thymol, and α-pinene; all of which exhibit insect repellent effects (Yang et al. 2004). These plant oils can be used as topical insect repellents and as oviposition deterrents (Gershenzon and Dudareva 2007).

Plant Products as Antifeedants

Antifeedants are substances with high vapor concentrations that alter behavior and inhibit feeding in insects. Many plants contain natural antifeedants to protect themselves against insect herbivory. There are several differences between repellents and antifeedants. A substance that provides a long duration of protection and lowers biting rate is considered both a highly efficient repellent and an antifeedant. However, a compound that confers protection for only a short time but lowers biting rate is considered more effective as an antifeedant than a repellent. In contrast, a product that provides long protection but does not lower biting rate is probably more effective as a repellent than an antifeedant (Phasomkusolsil and Soonwera 2011). Ali et al. (2015) demonstrated that essential oils in *Echinophora lamondiana* Yildiz & Z. Bahcecioglu had biting deterrent activity due to high levels of pure terpinolene.

Certain plant-based antifeedants prevent muscle contraction and feeding in insects (Ware 2000). Other antifeedants affect the taste organs (peripheral sensilla) of insects to deter them from feeding. Antifeedants can be sprayed in the field in the same way as pesticides.

Plant Products as Oviposition Deterrents

During oviposition, female mosquitoes rest on water surfaces at sites suitable for the growth of hatching larvae. Their antennas contain chemoreceptors that guide them towards appropriate oviposition sites (McBride et al. 2014). The eggs are laid individually on water surfaces either in natural or human-made environments, such as standing water in tires and vases (Wong et al. 2011). Mosquito populations can be controlled by preventing oviposition by using plants and various plant compounds. Therefore, these plant products could be used to control the spread of viruses transmitted by these mosquitoes (Da Silva Alves et al. 2015). Oviposition deterrence is quantified by the oviposition active index (OAI). OAI is calculated using the formula described by Kramer and Mulla (1979) and Xue et al. (2001): ER $(\%) = NC - NT/NC \times 100$ where ER = effective repellency, NC = control number of eggs, and NT = total number of eggs. Substances with OAI of <0.3 are considered repellents, whereas those with OAI of >0.3 are regarded as attractants. Plants and their products that function as oviposition deterrents are listed in Table 2, with citations arranged by publication year.

Table 2. Plant species with oviposition deterrent effects in the Zika virus vector *Aedes aegypti,* arranged by publication year.

Reference	Most Influential	Descriptors	Plant Species
Swathi et al. 2010	*D. stramonium* (ER = 100%)	Ethanolic extract of leaves	*Pongamia pinnata* *Coleus forskohlii* *Datura stramonium*
Siriporn and Mayura 2012	*C. odorata* (OAI = −1 at 10% concentration)	Essential oils	*Cananga odorata* *Cymbopogon citratus* *C. nardus* *Eucalyptus citriodora* *Ocimum basilicum* *Syzygium aromaticum*
Prathibha et al. 2014	*E. jambolana* (OAI = −0.93)	Extract (leaves/ flowers)	*Eugenia jambolana* *Solidago canadensis* *Euodia ridleyi* *Spilanthes mauritiana*
Ananth and Mani 2015	99.4% at 0.01 ppm	Extract (leaves)	*Acalypha ornata*
Reegan et al. 2015	Hexane extract of *L. acidissima* (ER = 100%)	Extract	*Aegle marmelos* *Limonia acidissima* *Sphaeranthus indicus* *Sphaeranthus amaranthoides* *Chromolaena odorata*
Da Silva, Milet-Pinheiro et al. 2015b	Oviposition rate dropped to 59–63% at 25, 50, and 100 ppm	Essential oils (leaves)	*Commiphora leptophloeos*
Soonwera 2015b	99.4% at 10% concentration	Flower oil	*Cananga odorata*
Yu et al. 2015	Methanol extract (OAI = −1 at 400 μg/mL)	Extracts (seaweed)	*Bryopsis pennata*
Benelli et al. 2016	OAI = −0.84 at 55.11 μg/ml	Essential oils	*Syzygium lanceolatum*
Bezerra-Silva et al. 2016	*n*-dodecanol (23.9% of total laid). 50 ppm	Analysis of oils	Essential oils of three cultivars of *Etlingera elatior*

Table 2. Continued.

Reference	Most Influential	Descriptors	Plant Species
AlShebly et al. 2017	ar-curcumene (OAI = −0.81 at 50 μg/ml)	Essential oils	*Hedychium larsenii*
Castillo et al. 2017	*E. citriodora* (OAI = −1.0 at 200 ppm)	Essential oils	*Lippia alba* *L. origanoides* *Eucalyptus citriodora* *Cymbopogon citratus* *Cymbopogon flexuosus* *Citrus sinensis* *Cananga odorata* *Swinglea glutinosa* *Tagetes lucida*
Govindarajan et al. 2018	(Z)-γ-bisabolene (OAI = ≤−0.79 at 25 μg/ml)	Essential oils	*Galinsoga parviflora*

OAI, oviposition active index; ER, percentage of effective repellency.

Conclusions

More than 2,000 plant species that belong to the Meliaceae, Rutaceae, Asteraceae, Cladophoraceae, Labiatae, and Apocynaceae families produce insecticidal chemicals (Ghosh et al. 2012, Shaalan et al. 2005). The effectiveness of products derived from the same plant may vary with the organ from which the products were extracted (Wannang et al. 2015). The type of solvent used for extraction can also determine the effectiveness of the plant product at eliminating mosquitoes. Examples of common solvents used in plant compound extraction are *n*-hexane, acetone, chloroform, ethyl acetate, and methanol. The median lethal concentrations (LC_{50}) of the extracts may vary with the type of solvent used possibly because of the differences in solvent composition and extraction ratio/efficiency (Ghosh et al. 2012, Shivakumar et al. 2013). Several studies have shown that extraction method influences the relative mosquito-controlling effectiveness of the plant extract. Plant extracts may be prepared by distillation using commercial oils or solvents (Kiplang'at and Mwangi 2014, Nasir et al. 2015, Soonwera 2015a, Sritabutra et al. 2011). Plant age (young, mature, old) can also affect the quality of the products extracted from collected samples (Fernandez et al. 2014).

A very important point we have tried to stress in this review is the lack of standardization of plant parts, extraction protocols, and other parameters used in the currently available studies. This limitation prevents us to reasonably compare the results of multiple studies. Methodological standardization could allow us to make these comparisons and accelerate the identification and development of plant-based mosquito-control agents. The present review categorized the bioactivity of mosquito-control compounds, which can guide the standardization of natural plant product classification.

Plants are rich sources of compounds that could improve disease vector control. Research efforts should focus on the development of plant products that can effectively control disease-bearing mosquitoes and be commercially applied as soon as testing confirms their long-term human, animal, and environmental safety. It is preferable to develop products that can be used at all stages of mosquito development (egg, larva, pupa, and adult) and that disrupt the insect life cycle. The plants selected for use as pest control product sources should be easily cultivated, accessible, cost-effective, and sustainable.

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