

Plant Extracts, Isolated Phytochemicals, and Plant-Derived Agents Which Are Lethal to Arthropod Vectors of Human Tropical Diseases – A Review

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Abstract



The recent scientific literature on plant-derived agents with potential or effective use in the control of the arthropod vectors of human tropical diseases is reviewed. Arthropod-borne tropical diseases include: amebiasis, Chagas disease (American trypanosomiasis), cholera, cryptosporidiosis, dengue (hemorrhagic fever), epidemic typhus (Brill-Zinsser disease), filariasis (elephantiasis), giardia (giardiasis), human African trypanosomiasis (sleeping sickness), isosporiasis, leishmaniasis, Lyme disease (lyme borreliosis), malaria, onchocerciasis, plague, recurrent fever, sarcocystosis, scabies (mites as causal agents), spotted fever, toxoplasmosis, West Nile fever, and yellow fever. Thus, coverage was given to work describing plant-derived extracts, essential oils (EOs), and isolated chemicals with toxic or noxious effects on filth bugs (mechanical vectors), such as common houseflies (*Musca domestica* Linnaeus), American and German cockroaches (*Periplaneta americana* Linnaeus, *Blattella germanica* Linnaeus), and oriental latrine/blowflies (*Chrysomya megacephala* Fabricius) as well as biting,

blood-sucking arthropods such as blackflies (*Simulium* Latreille spp.), fleas (*Xenopsylla cheopis* Rothschild), kissing bugs (*Rhodnius* Stål spp., *Triatoma infestans* Klug), body and head lice (*Pediculus humanus humanus* Linnaeus, *P. humanus capitis* De Geer), mosquitoes (*Aedes* Meigen, *Anopheles* Meigen, *Culex* L., and *Ochlerotatus* Lynch Arribalzaga spp.), sandflies (*Lutzomyia longipalpis* Lutz & Neiva, *Phlebotomus* Loew spp.), scabies mites (*Sarcoptes scabiei* De Geer, *S. scabiei* var *hominis*, *S. scabiei* var *canis*, *S. scabiei* var *suus*), and ticks (*Ixodes* Latreille, *Amblyomma* Koch, *Dermacentor* Koch, and *Rhipicephalus* Koch spp.). Examples of plant extracts, EOs, and isolated chemicals exhibiting noxious or toxic activity comparable or superior to the synthetic control agents of choice (pyrethroids, organophosphorous compounds, etc.) are provided in the text for many arthropod-vectors of tropical diseases.

Supporting information available online at <http://www.thieme-connect.de/ejournals/toc/plantamedica>

Introduction



Arthropod vectors of human tropical disease

Arthropods are the vectors of a variety of human diseases which affect tropical countries around the world (● **Table 1**) [1–22]. Biting, blood-sucking arthropods are the most important vectors in terms of public health. These include mosquitoes, tsetse flies [7], kissing bugs, sandflies, ticks, etc., which are responsible for the transmission of malaria, dengue hemorrhagic fever, filariasis [7], American [3–6] and Human African [7] trypanosomiasis, leishmaniasis [7, 13], spotted [7, 18], West Nile, and yellow fevers [7], among other se-

vere tropical diseases. Importantly, several dozens of species of anopheline mosquitoes are responsible for the transmission of the 4 *Plasmodium* parasite species which cause human malaria. According to data from the World Health Organization (WHO), half the world's human population lives in regions where malaria is endemic [7]. On the other hand, non-biting or non-blood-sucking coprophagic (feces-eating), saprophagic (living on decaying or decomposing materials), and other arthropods, such as dung beetles, common houseflies, and cockroaches can be mechanical vectors of amebiasis [1, 2], cholera [7, 8], cryptosporidiosis [1, 7], giardia [1, 10, 11], isosporiasis [12], sarcocystosis [1], toxoplasmosis [1, 16], and

Table 1 Human tropical diseases, etiological agents, and arthropod vectors.

| Tropical disease | | | Arthropod vector | | |
|---|---|---|-----------------------------|---|-------------|
| Name | Etiologic agent | Occurrence | Common name | Scientific name | Source |
| Amebiasis | <i>Entamoeba histolytica</i> , <i>E. dispar</i> | China, Mexico, S. America, S.-E. & W. Africa, S.-E. Asia | German cockroach | <i>Blatella germanica</i> Linnaeus | [1, 2] |
| | | | American cockroach | <i>Periplaneta americana</i> Linnaeus | |
| | | | Common housefly | <i>Musca domestica</i> Linnaeus | |
| Chagas disease (American trypanosomiasis) | <i>Trypanosoma cruzi</i> | Americas, Europe | Kissing bug | <i>Triatoma</i> , <i>Rhodnius</i> Stål spp., <i>Panstrongylus megistus</i> Burmeister | [3–6] |
| Cholera | <i>Vibrio cholerae</i> | Worldwide | Common housefly | <i>Musca domestica</i> Linnaeus | [7, 8] |
| Cryptosporidiosis | <i>Cryptosporidium</i> sp. | Africa, Asia, Australia, Europe, Americas | Dung beetle | <i>Onthophagus</i> Latreille, <i>Anoplotrupes</i> Jekel & <i>Aphodius</i> Illiger spp. | [1, 7] |
| | | | Common housefly | <i>Musca domestica</i> Linnaeus | |
| Dengue (hemorrhagic fever) | <i>Flavivirus</i> sp. | Africa, Americas, E. Mediterranean, S.-E. Asia & W. Pacific | Mosquito | <i>Ae. Aegypti</i> L., <i>Ae. Albopictus</i> Skuse | [7] |
| Epidemic typhus (Brill-Zinsser disease) | <i>Rickettsia prowazekii</i> | Africa, C. & S. America | Louse | <i>Pediculus humanus corporis</i> | [9] |
| Filariasis or Elephantiasis | <i>Wuchereria bancrofti</i> | Africa, Asia, S. America | Mosquito | <i>Aedes</i> Meigen, <i>Anopheles</i> Meigen, <i>Culex</i> L. spp. | [7] |
| Giardia, giardiasis | <i>Giardia lamblia</i> | Worldwide | German cockroach | <i>Blatella germanica</i> Linnaeus | [1, 10, 11] |
| | | | Common housefly | <i>Musca domestica</i> Linnaeus | |
| Human African trypanosomiasis (sleeping sickness) | <i>Trypanosoma brucei</i> | Africa | Tsetse fly | <i>Glossina</i> Wiedemann spp. | [7] |
| Isosporiasis | <i>Isospora belli</i> | Africa, Australia, Caribbean Islands, Latin America, S.-E. Asia | Dung beetle | <i>Onthophagus</i> Latreille spp. | [12] |
| | | | Common housefly | <i>Musca domestica</i> Linnaeus | |
| Leishmaniasis | <i>Leishmania</i> sp. | Asia, C. & S. America, E. Africa, Europe, India | Sandfly | <i>Lutzomyia</i> França, <i>Phlebotomus</i> Loew & <i>Sergentomyia</i> França & Parrot spp. | [7, 13] |
| Lyme disease (Lyme borreliosis) | <i>Borrelia</i> spp. | Asia, Europe, Americas | Tick | <i>Ixodes</i> Latreille, <i>Amblyomma</i> Koch spp. | [14, 15] |
| Malaria | <i>Plasmodium</i> spp. | Africa, Mexico, C. & S. America, Asia | Mosquito | <i>Anopheles</i> Meigen spp. | [7] |
| Onchocerciasis | <i>Onchocerca volvulus</i> | Africa, Mexico, C. & S. America | Blackfly | <i>Simulium</i> Latreille spp. | [7] |
| Plague | <i>Yersinia pestis</i> | Africa, Asia, Brazil, Bolivia, Peru, Ecuador, USA | Oriental rat flea | <i>Xenopsylla cheopis</i> Rothschild | [10] |
| Recurrent fever | <i>Borrelia recurrentis</i> | Africa, Asia, Europe, N. America | Louse | <i>Pediculus humanus</i> spp. | [14] |
| | | | Tick | <i>Ornithodoros</i> C. L. Koch spp. | |
| Sarcocystosis | <i>Sarcocystis</i> spp. | Worldwide | German cockroach | <i>Blatella germanica</i> Linnaeus | [1] |
| | | | American cockroach | <i>Periplaneta Americana</i> Linnaeus | |
| | | | Common housefly | <i>Musca domestica</i> Linnaeus | |
| Scabies | – | Worldwide | (Itch) Mite | <i>Sarcoptes scabiei</i> var <i>hominis</i> | [17] |
| Spotted fever | <i>Rickettsia rickettsii</i> | Brazil, Colombia, Mexico, Panama, Canada, USA | Tick | <i>Dermacentor</i> Koch, <i>Rhipicephalus</i> Koch, <i>Amblyomma</i> Koch spp. | [7, 18] |
| Toxoplasmosis | <i>Toxoplasma gondii</i> | Worldwide | Dung beetle | <i>Onthophagus</i> Latreille spp. | [1, 16] |
| | | | German cockroach | <i>Blatella germanica</i> Linnaeus | |
| | | | American cockroach | <i>Periplaneta americana</i> Linnaeus | |
| | | | Common housefly | <i>Musca domestica</i> Linnaeus | |
| | | | Oriental latrine or blowfly | <i>Chrysomya megacephala</i> Fabricius | |
| West Nile fever | <i>Flavivirus</i> sp. | Worldwide | Mosquito | <i>Culex</i> L. spp., <i>Ochlerotatus</i> Lynch Arribálzaga spp. | [7] |
| Yellow fever | <i>Flavivirus</i> sp. | Africa, Latin America | Mosquito | <i>Ae. aegypti</i> L., <i>Ae. albopictus</i> Skuse | [7] |

other infectious diseases and so must also be controlled for reasons of disease prevention and public health (● **Table 1**).

Literature on Plants for Arthropod Vector Control

In recent years, numerous scientific reports have been published on plants which are useful (or potentially useful) for the control of arthropod vectors of tropical diseases. Major emphasis has been on the most important arthropod-vector – the mosquito. Reviews

of the scientific literature have been published recently on mosquito larvicidal plant extracts and fractions [19], plant EOs exhibiting arthropod-killing (mosquitocidal, larvicidal) among other biological activities [20], and mosquito repellent and insecticidal plant EOs and chemical components [21–23]. The patent literature on plant EO-containing mosquito repellent inventions is also reviewed in this special issue of *Planta Medica* [24]. In the present review, emphasis is on literature published in the period 2007–2010 describing plant extracts and their active chemical components which cause the death of or are noxious to one or more of

the developmental stages (eggs, nymphs/larvae, pupae, adults) of a broad range of arthropod vectors of human tropical diseases such as blowflies, common houseflies, cockroaches, fleas, lice, mosquitoes, ticks, etc.

The plant sources of extracts, EOs, fractions, and isolated compounds which exhibit toxicity to, are noxious to, or are otherwise useful in the control of arthropods covered herein are terrestrial plants which generally have medicinal and other useful (economic) properties. Edible green and blue-green algae (cyanobacterium) having toxic properties towards insect species including larvae of *Aedes* Meigen, *Anopheles* Meigen, and *Culex* L. spp. were recently reviewed [25]. Thus, algae and aquatic plants are not covered herein nor are arthropod/insect control derivatives from bacteria and fungi (such as *Bacillus thuringiensis israelensis*, *B. sphaericus*, and *Saccharopolyspora spinosa*/Spinosa[®]) cultures.

Blackflies

The water extracts of the leaves of *Chromolaena odorata* (L.) R. M. King & H. Rob. exhibited lethality to larvae of *Simulium damnosum* Theobald (LC₅₀ = 1 µg/mL) which was not statistically different from that of the synthetic organophosphorous larvicide chlorpyrifos [26].

Hydrogenated catnip (*Nepeta cataria* L. leaf, stem) EO containing 15 weight-percent (wt%) of stereoisomeric dihydronepetalactones (1.67 g/m²) as active repellent ingredients was formulated into a liquid and a lotion both of which provided > 7.5 h mean complete protection against adult *Simulium decorum* Walker in the field [27].

Remarkably, in a field study in Thailand, the blackfly *Simulium nigrogilvum* Summers was effectively repelled by lotions containing 10% w/w EO in absolute ethanol (60%) and additives vanillin (10%), propylene glycol (10%), and polyethylene glycol (10%). Thus finger root (*Boesenbergia rotunda* [L.] Mansf.) EO, guava (*Psidium guajava* L.) leaf EO, and turmeric (*Curcuma longa* L.) EO were separately formulated into lotions which were tested together with the proprietary product Repel Care[®] (active ingredients: 5% w/w turmeric EO and 4.5% w/w *Eucalyptus citriodora* Hook. EO) and DEET (10% w/w lotion formulated as for EOs). All five formulations provided 100% protection for 9 h and > 82% for 10 and 11 h against *S. nigrogilvum* [28].

Blowflies

Topical application of eucalyptol (1,8-cineole) caused the death of *Chrysomya megacephala* Fabricius adult males and females (LD₅₀ = 197 and 221 µg/fly, respectively) [29]. Eucalyptol exhibited low activity against *C. megacephala* third instars (LD₅₀ = 642 µg/µL) using the dipping method. Also, *Azadirachta indica* A. Juss. seed extracts (containing 0.24% azadirachtin A) caused swelling of the protocoel of third instars and first stage pupae of *C. megacephala* by the dipping method [30]. Larvae of *C. megacephala* were effectively killed by betel (*Piper betle* L.) EO. At concentrations of 3–4% betel EO, 100% larvae mortality was observed [31]. Nine plant EOs were screened for ovicidal activity against *C. megacephala* and *Eugenia caryophyllata* Thunb., *Illicium verum* Hook. f. and *Cinnamomum cassia* (L.) C. Presl EOs exhibited the most activity (LC₅₀ = 1.61, 2.49, and 0.43 mg/mL, respectively). Also, synthetic cinnamaldehyde showed ovicidal activity (LC₅₀ = 0.28 mg/mL) [32].

Cockroaches

Pure components from EOs were screened for lethality against different developmental stages of *Blattella germanica* Linnaeus [34]. Topically applied pure components caused the death of adult males, females, gravid females, and nymphs at different stages of development of *B. germanica*. The most active substances against *B. germanica* adult males were thymol, *E*-cinnamaldehyde, carvacrol, and eugenol (LD₅₀ = 0.070, 0.078, 0.101, 0.109 mg/cockroach, respectively). Against *B. germanica* adult females the most active substances were carvacrol, *E*-cinnamaldehyde, and thymol (LD₅₀ = 0.186, 0.188, and 0.195 mg/cockroach, respectively), and these same substances were also the most active against gravid *B. germanica*: thymol > *E*-cinnamaldehyde > carvacrol (LD₅₀ = 0.122, 0.133, and 0.146 mg/cockroach, respectively).

Large *B. germanica* nymphs were also susceptible to topical treatment with EO components, and for large nymphs the most active substances were *E*-cinnamaldehyde, carvacrol, and thymol (LD₅₀ = 0.117, 0.129, and 0.220 mg/cockroach, respectively) while for medium nymphs the most active substances were thymol, carvacrol, *E*-cinnamaldehyde, and eugenol (LD₅₀ = 0.060, 0.061, 0.082, and 0.109 mg/cockroach, respectively) [34]. Small *B. germanica* nymphs were the most sensitive to natural components of EOs, and substances exhibited activity in the following order: *E*-cinnamaldehyde > thymol ~ geraniol > carvacrol ~ *S*-(-)-limonene > (-)-menthone (LD₅₀ = 0.036–0.060 mg/cockroach). Diminished nymph hatching was observed for *B. germanica* eggs treated with (-)-menthone. Based on these and other data, the group of substances thymol, *E*-cinnamaldehyde, carvacrol, geraniol, and eugenol exhibited interesting lethality to different stages of development of *B. germanica* [34].

Using a T-tube olfactometer, 17 EOs were screened, and 5 EOs exhibited significant repellency against *B. germanica* and other cockroach species. Thus, adult female *Periplaneta americana* Linnaeus (American cockroach) and *B. germanica* (German cockroach) were repelled by grapefruit (*Citrus × paradisi* Macfad.), lemon (*Citrus × limonum* Risso), lime [*Citrus × aurantiifolia* (Christm.) Swingle], orange [*Citrus × sinensis* (L.) Osbeck] EOs by 90.3, 85.7, 83.3, and 70.0%, respectively, and 96.7, 92.9, 86.7, and 71.4%, respectively [33]. Adult female *B. germanica* were also repelled by clove leaf (*Eugenia caryophyllata* Thunb.) EO (repellency = 70.0%). Another cockroach, *Periplaneta fuliginosa* Serville, was less repelled by these *Citrus* L. spp. EOs: 82.4, 72.0, 70.6, and 62.5%, respectively. Yoon et al. [33] identified two different “types” of *Citrus* oils based on the relative quantity of the components limonene (> 90% = type I = grapefruit and orange EOs; 48–61% = type II = lemon and lime EOs) and α -pinene, β -pinene, γ -terpinene, β -myrcene, and benzene. Generally, type I EOs exhibited repellencies which could be reproduced by placing the volume of pure limonene present in 10 µL of EO in the olfactometer for both *B. germanica* and *P. americana*. To study the effects of type II EOs, limonene (6.4 µL) combined with β -pinene (1.4 µL) was found to provide repellency (90.3%) comparable to that of 10 µL of lemon and lime (type II) EOs against *B. germanica*. Adult female *B. germanica* were repelled about equally by limonene (ca. 6.1 µL) + β -pinene (1.6 µL) or 10 µL of type II (lemon and lime) EOs. In a ternary mixture of limonene + β -myrcene + γ -terpinene (6.1 + 0.1 + 0.4 µL), a repellency of 83.3% was attained which was comparable to the type II EO repellency against adult female *B. germanica*. When the individual components were tested for repellency against *P. americana* adult females in the volumes present in 10 µL of type II EOs, β -pinene (1.17 µL) fully repro-

duced the repellency of 10 μL of lime EO. For type II EOs, to reproduce the repellent effect of 10 μL of lime and lemon EOs to adult *P. americana*, only ternary combinations of limonene (6.1 μL) + γ -terpinene (0.4 μL) + [either β -myrcene (0.1 μL), β -pinene (1.4 μL), or α -pinene (0.2 μL)] produced repellencies (80–83%) comparable to those of both type II EOs [33]. This work demonstrates the very complex synergistic and suppressive interactions among the monoterpenes in these *Citrus* EOs and the species specific nature of repellency in these cockroach species.

Common houseflies

Solvent extracts of plants and isolated chemical components have been tested for important control effects mainly against mature *Musca domestica* Linnaeus. Thus, seed and root petroleum ether extracts of *Griffonia simplicifolia* (M. Vahl ex DC.) Baill. and root and stem petroleum ether extracts of *Zanthoxylum xanthoxyloides* (Lam.) Waterman repelled (median repellent doses, RD_{50} = 1.0–1.7 $\mu\text{g}/\text{cm}^2$) and killed mature *M. domestica* (topical LC_{50} = 0.3–0.5 $\mu\text{g}/\text{fly}$) [35]. In other work, EtOH extracts of *A. indica* which contain the active ingredient azadirachtin A were found to be highly lethal to adult flies (94% mortality) at a concentration of 0.025%, but were only moderately lethal to earlier stages (larvae, pupae) even at higher concentrations [30]. Coumarin was isolated from the hexane extract of the leaves of *Ageratum conyzoides* L. and shown to be highly toxic (LD_{50} = 1.2, LD_{90} = 3.7 mg/g) to mature *M. domestica* [36]. Also, friedelin was isolated from *Cacalia tangutica* (Maxim.) Hand.-Mazz. extract and (as a coating on sugar) was found to be as lethal (LC_{50} = 0.130 mg/g sugar) to mature *M. domestica* as rotenone (LC_{50} = 0.091 mg/g sugar) which was used as control substance [37]. These examples demonstrate the potential of plant extracts and their active principles as sources of control agents for mature *M. domestica*.

A number of plant EOs and volatile chemical components exhibiting adulticidal activity against *M. domestica* have been identified in recent publications. *Eucalyptus* L'Hér. spp., *Citrus* \times *sinensis* (L.) Osbeck, *Lavandula angustifolia* Mill., *Mentha* L. spp., and *Pelargonium graveolens* L'Hér. EOs were found to effectively knock down and kill *M. domestica* (KT_{50} = 3–18 min; LD_{50} = 0.07–0.16 $\mu\text{g}/\text{insect}$) [38]. Several of the isolated monoterpenes of these EOs, namely 1,8-cineole (KT_{50} = 2.3 min, LD_{50} = 0.13 $\mu\text{g}/\text{insect}$), limonene (KT_{50} = 7.5 min, LD_{50} = 0.10 $\mu\text{g}/\text{insect}$), linalool (KT_{50} = 7.6 min, LD_{50} = 0.04 $\mu\text{g}/\text{insect}$), menthone (KT_{50} = 19.0 min, LD_{50} = 0.11 $\mu\text{g}/\text{insect}$), and menthyl acetate (KT_{50} = 22.6 min, LD_{50} = 0.09 $\mu\text{g}/\text{insect}$) were found to be toxic to *M. domestica* [38]. However, an independent study on 1,8-cineole found much lower lethal doses against *M. domestica* mature males (LD_{50} = 118 $\mu\text{g}/\text{fly}$) and females (LD_{50} = 177 $\mu\text{g}/\text{fly}$) [29]. In another screening for fumigant activity, *C. sinensis*, *Citrus* \times *aurantium* L., *Citrus* \times *limonum* Risso, *Citrus* \times *paradisi* Macfad., *Citrus* \times *reticulata* Blanco, *Coriandrum sativum* L., *Eucalyptus cinerea* F. Muell. ex Benth., *Laurus nobilis* L., and *Myristica fragrans* Houtt. EOs were found to be active (LC_{50} = 3.9–8.8 mg/ cm^3) against mature *M. domestica*, and several of the monoterpene components of these EOs were evaluated for activity against *M. domestica*. Besides 1,8-cineole (LC_{50} = 3.3 mg/ dm^3), (–) and (+)-limonene (LC_{50} = 5.0 and 6.2 mg/ dm^3 , respectively), chemical components such as γ -terpinene (LC_{50} = 4.0 mg/ dm^3), α -terpinene (LC_{50} = 6.2 mg/ dm^3), citronellal (LC_{50} = 8.1 mg/ dm^3), (–)- β -pinene (LC_{50} = 6.4 mg/ dm^3), and (–)- α -pinene (LC_{50} = 8.9 mg/ dm^3) were also found to be toxic to mature *M. domestica* [39]. Phenylpropanoids are another class of volatile compounds having important lethality to *M. domestica*. In a

recent study on the lethality of the EO and chemical components from the leaves of *Piper betle* L. to *M. domestica*, EO (LC_{50} = 10.3 mg/ dm^3) and individual phenylpropanoid EO components safrole (LC_{50} = 4.8 mg/ dm^3), dihydrosafrole (LC_{50} = 4.7 mg/ dm^3), isosafrole (LC_{50} = 2.3 mg/ dm^3), and eugenol (LC_{50} = 7.3 mg/ dm^3) all proved to have significant toxicity to mature *M. domestica* [40].

In the Supporting Information, data from literature sources on plant extracts, EOs, monoterpenes, and phenylpropanoids exhibiting fumigant and other activities against *M. domestica* are presented.

Dung beetles

No recent studies on plant extracts, oils, or chemical components for the control of *Anoplotrupes* Jekel & *Aphodius* Illiger spp. of dung beetles were found. This could be an interesting group for future study given that these filth-associated organisms exist in many countries around the world where basic hygiene and coexistence with these species may be a source of contamination and infections (● Table 1).

Fleas

Incense cedar (*Calocedrus decurrens* [Torr.] Florin) heartwood EO (LC_{50} = 0.24, LC_{90} = 0.31 mg/mL), Port-Orford [*Chamaecyparis lawsoniana* (A. Murray) Parl.] cedarwood EO (LC_{50} = 1.21, LC_{90} = 1.85 mg/mL), and western juniper (*Juniperus occidentalis* Hook.) heartwood EO (LC_{50} = 0.31, LC_{90} = 0.93 mg/mL) exhibited adulticidal effects on *Xenopsylla cheopis* Rothschild fleas [41].

Isolated components from Alaska yellow cedar (*Chamaecyparis nootkatensis* [D. Don] Spach) heartwood EO, derivatives, and commercially acquired products were tested against *X. cheopis*. Carvacrol, valencene, nootkatene, crystalline nootkatone, nootkatone grapefruit extract, isolated nootkatone, valencene-13-ol, nootkatol, valencene-13-aldehyde, nootkatone 1,10 epoxide, nootkatone diepoxide all were active against *X. cheopis* exhibiting LC_{50} = 0.0029–0.064% w/v and LC_{90} = 0.0049–0.10% w/v 24 h after exposure. Nootkatone (grapefruit EO) was the most active sample tested (LC_{50} = 0.0029, LC_{90} = 0.008% w/v) [42].

Kissing bugs (assassin bugs, bloodsucking conenoses, “barbeiros”)

24 plant extracts were screened for insecticidal activity against fourth stage blood-replete nymphs of *Rhodnius milesi* Carcallo, Rocha, Galvão & Jurberg by applying 50 μg of each extract to the abdomen of the nymphs. Hexane and ethanol extracts of *Simarouba versicolor* A.St.-Hil., *Guarea kunthiana* A. Juss., *G. guidonia* (L.) Sleumer, and *Talauma ovata* A.St.-Hil. caused 20–95% mortality among nymphs, and the ethanol extract of the root bark of *S. versicolor* and hexane extract of the roots of *G. guidonia* were responsible for 95 and 75% nymph mortalities, respectively [43].

Topically applied *Pilocarpus spicatus* A. St.-Hil. leaf EO was toxic to and paralyzed *Rhodnius prolixus* Stål fifth stage male nymphs (0.5 and 1.0 μL EO/insect, 90.5 and 91.1% mortality, respectively, after 24 h; 89 and 92% paralysis of surviving nymphs after 15 days) as well as retarded moulting and had partial antifeedant effects [44]. In other work, EOs and monoterpenes were screened for fumigant activity (exposure to vapors emitted by 100 μL of EO or monoterpene in a closed vessel) against *R. prolixus* first instars. Eucalyptus EO was the most active fumigant (KT_{50} = 216 min) and eucalyptol (1,8-cineole) was the most active fumigant monoterpene (KT_{50} = 117 min) [45].

In the above work, EOs and monoterpenes were also screened for repellency against *R. prolixus* first instars. Thus, mint and lavender EOs produced slight repellent effects at 400 $\mu\text{g}/\text{cm}^2$; geraniol and menthyl acetate produced slight repellent effects, respectively, at 40 and 400 $\mu\text{g}/\text{cm}^2$; and menthone produced a slight repellent effect at 400 $\mu\text{g}/\text{cm}^2$ [45].

Schinus molle L. leaf and root hexane extracts exhibited greater repellency than DEET against first instars of blood-sucking cone-noses *Triatoma infestans* Klug. Also, 3% w/v (maximum concentration tested) hexane extract of the fruit of *S. molle* caused 80% inhibition of hatching of *T. infestans* eggs [46].

Lice

Hedychium spicatum Buch.-Ham. ex Sm. rhizome EO at 1–5% concentrations exhibited pediculicidal activity against human body lice (*Pediculus humanus humanus*) which was greater than a 1% permethrin based product which was tested for comparison [47]. In other work, head lice (*P. humanus capitis*) were killed by the ethyl acetate extracts of the seeds of custard apple (*Annona squamosa* L.), and the hexane extract of seeds contains oleic acid (13.88 wt%) and a triglyceride with one oleate ester (7.70 wt%). Ethyl acetate extract, oleic acid, and triglyceride with one oleate ester were diluted (1 : 1) in inactive coconut oil and found to kill clinically obtained *P. humanus capitis* in 31.7, 47.3, and 10.0 min, respectively [48]. In another study involving clinically-obtained third instars and adult head lice (*P. humanus capitis*), 1,8-cineole was found to inhibit acetylcholine-esterase in a homogenate of *P. humanus capitis* and was found also to cause intoxication (knockdown) after 20 min of exposure to 1,8-cineole vapor. This result was better than contact with the standard lice control compound DDVP (dichlorvos) which after 60 min of exposure had only knocked down 50% of head lice [49]. This same group of researchers tested 23 monoterpenoid compounds for ovicidal and fumigant activity (adulticide activity) in permethrin-resistant *P. humanus capitis*. Of 6 monoterpenes screened, only (+)- α -pinene (KT_{50} = 34.5 min) and (-)- α -pinene (KT_{50} = 28.5 min) had fumigant activity against adult *P. humanus capitis* [50]. These authors compared this result to previous work by the group in which 1,8-cineole (KT_{50} = 11.1 min), anisole (KT_{50} = 12.7 min), limonene (KT_{50} = 27.2 min), β -pinene (KT_{50} = 33.9 min), linalool (KT_{50} = 37.7 min), menthone (KT_{50} = 39.7 min), α -pinene (KT_{50} = 42.7 min), and benzyl alcohol (KT_{50} = 59.7 min) were shown to be active fumigants against adult *P. humanus capitis*.

Louse egg mortalities > 80% relative to negative controls were obtained for anisole (100%), α -pinene (97%), β -pinene (96%), (+)- α -pinene (96%), 1S(-)- α -pinene (94%), anethole (93%), carvone (92%), limonene (90%), linalool (88%) and 1,8-cineole (84%) [50]. These results demonstrate the potential use of monoterpenes and other substances in the control of permethrin-resistant head lice.

Mosquitoes

Several recent reviews have been published on mosquito control agents from plants and related topics. In 2010, Nerio et al. [23] published a review on mosquito-repellent EOs and their repellent components. Both Bakkali et al.'s 2008 review [20] on the biological activity and toxicity of EOs and components and Burfield & Reekie's (2005) review [21] on EOs and components for mosquito control included data from publications on larvicidal, adulticidal, and other biological activities related to mosquito control. In the present work, the literature on plant extracts, fractions, and isolated chemical components having useful biological activ-

ities for mosquito control were reviewed. Given the large number of publications, emphasis was given to literature describing the lethal activity of isolated phytochemicals against mosquitoes. As Supporting Information, adulticidal, larvicidal, and ovicidal activities and other effects of plant extracts, essential oils, and fractions are summarized for publications which failed to report biological activity for isolated component chemicals (active principles) and which were not covered in this review. Also, Supporting Information includes data on extracts, EOs, and fractions as well as most nonvolatile active components discussed in this review. Publications on active extracts and essential oils having at least one (isolated) active principle which is potentially relevant for the purpose of mosquito control are discussed below.

Mosquitocides

EOs and their isolated components which exhibit important fumigant activity in knockdown and adulticide assays against mosquito species have been the subject of recent publications. Kiran and Devi [88] described fumigant activity of *Chloroxylon swietenia* DC. EO to adult *An. gambiae*, *Cx. quinquefasciatus*, and *Ae. aegypti* (LD_{50} = 1.0, 1.2, and 1.7 $\mu\text{g}/\text{cm}^3$, respectively; KT_{50} = 0.32, 0.50, and 0.72 h, respectively). This fumigant activity was attributed to sesquiterpene components present in the EO such as germacrene D (LD_{50} = 1.8, 2.1, and 2.8 $\mu\text{g}/\text{cm}^3$, respectively) which was purportedly acting synergistically with other components in the EO (EO was more active than these individually tested components) (Table 4). In other work, *Eucalyptus* spp. EOs exhibited general efficiency in knocking down adult *Ae. aegypti* (KT_{50} = 4–12 min), which was associated with the presence of 1,8-cineole and other components in the EOs (Table 4) [89]. These authors also confirmed the relationship between the vapor pressure of *Eucalyptus* spp. EOs and highly active individual components such as 1,8-cineole, α -pinene, and *p*-cymene and median knockdown time (KT_{50}) in *Ae. aegypti* adult mosquitoes. *Mentha × piperita* L. was also found to be highly active against mature *Ae. aegypti* [90]. *Chloroxylon swietenia*, *Eucalyptus* spp., and *Mentha × piperita* EOs contain a number of volatile mosquitocidal chemical components whose fumigant activity was investigated in the above studies and is summarized in Table 4. Knockdown times of just 4–6 min were observed for 1,8-cineole, *p*-cymene, and α -pinene (*Eucalyptus* spp.) against mature *Ae. aegypti* while mugetanol, α -terpineol, and thymol (found in *Mentha* L. spp. EO) were highly effective at knocking down and killing mature *Ae. aegypti*, *An. tessellates* Theobald, and *Cx. quinquefasciatus*. Interestingly, L-menthol was found not to be toxic to adult *Ae. aegypti* [90]. This is a reminder that molecular and taxonomic specificities may be important characteristics of the toxic effects of certain mosquitocidal substances.

Mosquito larvicides

A. indica or neem oil formulations are important mosquito control agents, and a formula containing 0.15% of the limonoid azadirachtin was tested and found to be highly effective at killing *Ae. aegypti* (LC_{50} = 1.7 ppm) and *An. stephensi* Liston (LC_{50} = 1.6 ppm) in the lab and *Aedes* spp. (95–100% reduction of larvae over 7 days), *Anopheles* spp. (80–100% reduction of larvae over 3 weeks), and *Culex* spp. (\geq 80% reduction of larvae over 3 weeks) in the field [51]. For another formulation comprised of wood and bark chips of neem tree (*A. indica*) in water, effective larvicidal activity was observed against first thru fourth instars of *An. gambiae* (IE_{90} = 0.12–0.6 g wood chips/L H_2O) [52]. Interestingly, no azadirachtin was found in these aqueous solutions; however,

the limonoids nimbin and salannin were detected by HPLC analysis by comparison with authentic samples. As these and earlier studies have demonstrated, *A. indica* (neem) derivatives, especially neem oil and the active ingredient azadirachtin, show great promise as general plant-based mosquitocides and larvicides and are the basis for a number of commercially available products.

The limonoid calodendrolide was isolated from the root bark of *Calodendrum capense* Thunb. and was reduced to pyroangolenolide. These two limonoids exhibited important larvicidal activity against *Ae. aegypti* (LC_{50} = 13.2 and 16.6 μ M, respectively). In this same work, the authors also isolated the limonoids harrisonin and pedonin from the methanol extract of the root bark of *Harrisonia abyssinica* Oliv. and demonstrated that these two compounds had activity against *Ae. aegypti* larvae (LC_{50} = 28.1 and 59.2 μ M, respectively) [53]. Two quassinoids, neosergeolide and isobrucein B, were isolated from the roots and stems of the Amazonian medicinal plant *Picrolemma sprucei* Hook. f. and exhibited good larvicidal activity against *Ae. aegypti* (LC_{50} = 8.7 and 6.7 μ M, respectively) [54].

The sesquiterpenes cubebol (LC_{50} = 68.6 and 50.0 μ g/mL against *Ae. aegypti* and *Ae. albopictus* Skuse, respectively) and *epi*-cubebol (LC_{50} = 100 and 63.8 μ g/mL against *Ae. aegypti* and *Ae. albopictus*, respectively) together with ferruginol (LC_{50} = 64.1 μ g/mL against *Ae. aegypti*) were isolated from the wood extract of *Cryptomeria japonica* (Thunb. ex L.f.) D. Don [55]. Sesquiterpenoid metabolites 9-oxoneoprocumeneol (LC_{50} = 5.81 ppm) and neoprocumeneol (LC_{50} = 13.7 ppm) exhibited larvicidal activity against *Cx. quinquefasciatus* Say and were isolated from the petroleum ether extract (LC_{50} = 11.4 ppm) of wild turmeric (*Curcuma aromatic* Salisb.) root [56].

A group from Brazil described the larvicidal activity (LC_{50} = 8.9 ppm) of the oil-resin from the trunk of *Copaifera reticulata* Ducke against *Ae. aegypti* and also the successful fractionation of the oil-resin to obtain active sesquiterpene (LC_{50} = 0.2 ppm) and labdane-enriched (LC_{50} = 0.8 ppm) fractions [57]. Later, this group reported the isolation of mosquito larvicidal diterpenes 3- β -acetoxylabdan-8(17)-13-dien-15-oic acid (LC_{50} = 0.8 ppm) and alepterolic acid (LC_{50} = 87.3 ppm) [58].

Rahuman et al. [59] isolated the tetracyclic triterpene derivative gluanol acetate from the acetone extract of the bark of *Ficus racemosa* L. and found that it had important larvicidal activity against *Ae. aegypti*, *An. stephensi*, and *Cx. quinquefasciatus* fourth instars (LD_{50} = 14.6, 28.5, and 41.4 ppm, respectively).

The dichloromethane extract of the root bark of the traditionally used mosquito repellent plant *Lantana viburnoides* subsp. *viburnoides* var. *kisi* had potent larvicidal activity against *An. gambiae* Giles s.s. (72 h LC_{50} = 7.70 ppm). Active fractions of this extract contained the lantadene-type triterpene camaric acid (72 h LC_{50} = 6.19 ppm) and the lupine triterpene betulinic acid (72 h LC_{50} < 10 ppm) [60].

The steroid β -sitosterol was isolated from the petroleum ether extracts of the leaves of *Abutilon indicum* (Linn.) Sweet [61] and a saponin of unknown identity was isolated from *Achyranthes aspera* L. [62], and both exhibited significant toxicity to *Ae. aegypti* larvae (LC_{50} = 11.5 ppm and 18.2 ppm, respectively) and *Cx. quinquefasciatus* larvae (LC_{50} = 26.7 ppm and 27.2 ppm, respectively). β -Sitosterol was further found to be a larvicide against *An. stephensi* (LC_{50} = 3.58 ppm) [61]. A phytosteroid of unknown identity was isolated from the juice of crushed fresh leaves, and 50 ppm of this substance killed 83, 93, and 100% of *Cx. quinquefasciatus* larvae after 24, 48, and 72 h, respectively [63].

Anthraquinone and naphthoquinone larvicides have been described in recent literature. Thus, using bioguided fractionation in the search for larvicidal compounds against *Ae. aegypti* and *Ae. albopictus*, Cheng et al. isolated the anthraquinone tectoquinone (LC_{50} = 3.3 and 5.4 μ g/mL, respectively) from the highly active hexane fraction (LC_{50} = 2.4 and 3.3 μ g/mL, respectively) of the methanol extract of the sapwood of *Cyptomeria japonica* (Forssk.) Vahl [64]. From the ethyl acetate extracts of the leaves of *Cassia nigricans* Vahl, the anthraquinones emodin (LC_{50} = 2.4 μ g/mL after 48 h), citreoresin (LC_{50} = 7.67 μ g/mL after 48 h), and emodic acid (LC_{50} = 2.88 μ g/mL after 48 h) were isolated and found to be highly active larvicides against *An. gambiae* [65].

From the chloroform extracts of the rhizomes of *Plumbago capensis* Thunb. naphthoquinones and naphthoquinone dimers isoshinanone (LC_{50} = 1.26 μ g/mL), plumbagin (LC_{50} = 5.43 μ g/mL), 3-O-methylhydroserone (LC_{50} = 31.5 μ g/mL), 6-hydroxyplumbagin (LC_{50} = 13.6 μ g/mL), maritinone (LC_{50} = 40.7 μ g/mL), and chitranane (LC_{50} = 31.2 μ g/mL) were isolated and found to be larvicidal to *Ae. aegypti* [66]. In other work, *Plumbago dawei* Rolfe ethyl acetate, *P. stenophylla* Wilmot-Dear chloroform, and *P. zeylanica* L. hexane and chloroform extracts of root barks exhibited strong larvicidal activity against *An. gambiae* (LC_{50} = 4.1–6.7 μ g/mL), and plumbin was isolated and confirmed as a potent *An. gambiae* larvicide (LC_{50} = 1.9 μ g/mL) [67]. Also, from the dichloromethane extract of the root bark of *Lantana viburnoides* subsp. *viburnoides* var. *kisi*, which was shown above to contain mosquito larvicidal triterpenes, one of the active fractions contained furanoquinone regioisomers (72 h LC_{50} = 5.48–5.70 ppm) [60].

Plants from the Brazilian cerrado biome were screened for larvicidal activity against *Ae. aegypti*, and the most active species found was *Ocotea velloziana* (Meisn.) Mez. The ethanol extract of the trunk bark (LC_{50} = 214 μ g/mL) was fractionated using biomonitoring to yield the larvicidal aromatic alkaloid (+)-dicentrine (LC_{50} = 30.2 μ g/mL) [68].

Fatty acids can have important larvicidal effects against different mosquito species. Thus, oleic and linoleic acids (LC_{50}/LC_{90} = 8.8/35.4 and 18.2/96.3 ppm, respectively) were isolated from the petroleum ether extracts of *Citrullus colocynthis* (L.) Schrad. and were shown to be the active larvicidal principles against *Cx. quinquefasciatus* [69]. These fatty acids are readily available from (saponified) fats and glyceridic oils, and they deserve more attention and study to establish their potential as mosquito larvicides. Plant proteins also can be important mosquito larvicides. A water soluble lectin was purified from the water extracts of the seeds of *Moringa oleifera* Lam. and shown to retard development and kill *Ae. aegypti* (LC_{50} = 0.197 mg/mL) larvae [70]. In other work, from the 0.15 M NaCl extracts of *Myracrodruon urundeuva* Allemão bark and heartwood, lectins were isolated and found to have high larvicidal activity against *Ae. aegypti* (LC_{50} = 0.125 and 0.040 mg/mL, respectively) [71]. Lastly, from the water extract of the fresh leaves of *Solanum villosum* Mill., a protein was isolated and purified and shown to have larvicidal activity against *Ae. aegypti*, *An. stephensi*, and *Cx. quinquefasciatus* (LC_{50} = 747, 645, and 646 ppm, respectively) [72].

Mosquito larvicidal compounds representing other chemical classes have been identified recently. For example, ethanol extracts of the roots of *Tephrosia toxicaria* (Sw.) Pers. exhibited larvicidal activity against *Ae. aegypti* (LC_{50} = 47.9 ppm) as did the hexane, chloroform, and ethyl acetate fractions (LC_{50} = 13.8–95.5 ppm). α -Toxicarol was isolated and shown to have larvicidal activity against *Ae. aegypti* (LC_{50} = 24.6 ppm) [73]. In other work, galloannin was isolated from the ethyl acetate extracts of *Quer-*

cus infectoria G. Olivier galls and was found to have larvicidal activity ($LC_{50} = 125$ ppm) against *An. stephensi* [74]. Also, *Piper peltatum* L. root ethanol extract exhibited only slight lethality to *Ae. aegypti* third instars after 24 h [75]; however, based on isolated yields, this dry root can contain at least 5.7% w/w 4-nerolidylcatechol which is lethal ($LC_{50} = 26.0$ $\mu\text{g/mL}$) to *Ae. aegypti* larvae [76].

In recent work, chemical components of plant EOs which are toxic to mosquito larvae have been described. For example, from the leaf and twig EO of *Piper aduncum* L., the volatile phenylpropanoid compound dillapiol was isolated and shown to be toxic to *Ae. aegypti* larvae ($LC_{50} = 36.2$ $\mu\text{g/mL}$). Furthermore, isodillapiol ($LC_{50} = 21.7$ $\mu\text{g/mL}$) and *n*-propyloxy and *n*-butyloxy propan-2-yl ether derivatives ($LC_{50} = 28.0$ and 19.7 $\mu\text{g/mL}$, respectively) prepared from dillapiol are more active larvicides than dillapiol [76]. Through compositional studies on the larvicidal EO of the roots of *Asarum heterotropoides* F. Schmidt (against *Ae. aegypti*, *Cx. pipiens pallens* Coquillet, and *Ochlerotatus togoi* Theobald, $LC_{50} = 23.8$, 21.1 , and 27.6 ppm, respectively), the major components were identified and found to be terpenoid and phenylpropanoid compounds. These components were individually tested for activity against mosquito larvae. Thus, 3-carene, (+)-limonene, α -phellandrene, safrole, γ -terpinene, and terpinolene were found to be highly toxic to *Ae. aegypti*, *Cx. pipiens pallens*, and *Oc. togoi* larvae (Table 2) [77]. Independently, R-limonene ($LC_{50} = 37$ ppm) was shown to be the most important larvicidal active principle of the leaf EOs of *Lippia gracilis* Schauer against *Ae. aegypti* [78], but several other active substances were also found (Table 2). In studies on the composition and larvicidal activity of *Clausena excavata* Burm. f. leaf and twig EOs ($LC_{50} = 37.1$ and 40.1 $\mu\text{g/mL}$, respectively, against *Ae. aegypti*; $LC_{50} = 41.2$ and 41.1 $\mu\text{g/mL}$, respectively, against *Ae. albopictus*) [79], *Cryptomeria japonica* leaf EO ($LC_{50} = 28.4$ and 51.2 $\mu\text{g/mL}$ against *Ae. aegypti* and *Ae. albopictus*, respectively) [80], and *Eucalyptus camaldulensis* Dehnh. and *E. urophylla* S.T. Blake leaf EOs ($LC_{50} = 31.0$ and 95.5 $\mu\text{g/mL}$, respectively, against *Ae. aegypti*) [81], 3-carene (against *Ae. aegypti*) [79], (+)-limonene (against *Ae. aegypti*) [79, 81], *p*-cymene (against *Ae. aegypti* and *Ae. albopictus*) [80, 81], α -phellandrene (against *Ae. aegypti*) [81], myrcene (against *Ae. aegypti* and *Ae. albopictus*) [79, 80], and α -terpinene (against *Ae. aegypti*) [81] were also found to be highly active larvicides ($LC_{50} < 20$ ppm) (Table 2).

The leaf EOs of 6 chemotypes of *Cinnamomum osmophloeum* Kaneh. were studied, and two chemotypes with expressive larvicidal activity against *Ae. albopictus* ($LC_{50} = 40.8$ – 46.5 $\mu\text{g/mL}$) and one with expressive activity against the larvae of *Cx. quinquefasciatus* ($LC_{50} = 31.3$ $\mu\text{g/mL}$) were described. Also, components of *C. osmophloeum* EOs such as *E*-cinnamaldehyde, benzaldehyde, and cinnamyl acetate were individually tested and found to exhibit significant larvicidal activity [82]. Diallyl disulfide (from *Allium sativum* L.) [83] and linalyl acetate (from *Citrus × aurantium*) [84] also exhibit important larvicidal effects (Table 2).

Thyme (*Thymus vulgaris* L.), parsley (*Petroselinum crispum* [Mill.] Fuss), anise (*Pimpinella anisum* L.), and coriander (*Coriandrum sativum* L.) EOs exhibited larvicidal activities ($LC_{50} = 15.0$, 34.3 , 65.1 , and 156 $\mu\text{g/mL}$, respectively) against the seaside mosquito species *Ochlerotatus caspius* Pallas. Eugenol, thymol, carvacrol, *trans*-anethole, and linalool, which are components of these EOs, exhibited larvicidal activity (Table 2) [85].

Interestingly, the larvicidal activity of each of the enantiomers of α and β -pinene was studied. In general (–)- β -pinene was found to be the most toxic ($LC_{50} = 13$ – 37 ppm) to the larvae of *Ae. aegypti*,

Cx. pipiens pallens and *Oc. togoi* [77], and *Cx. pipiens* biotype *molestus* [86]. Enantiomeric composition, especially in components of EOs, is an important and often neglected aspect of the study of insecticide interactions. Substances such as linalool, limonene, etc., occur in EOs in one or both enantiomeric forms and the enantiomeric composition of the commercially supplied substance (often used in biological testing) is not necessarily the same as that of the enantiomeric composition of this component in the EO of a given plant under study. The identification of these larvicidal active components in *in vitro* studies is significant and requires further work to evaluate the potential of these components in formulations, their acceptability to humans, and their toxicity to humans and to mosquitoes in field settings.

From the data presented in Table 2 on recent studies on the larvicidal activity of components of EOs against mosquito species, the monoterpenes β -asarone, *p*-cymene, (+)-limonene, linalyl acetate, myrcene, α -phellandrene, (+)- β -pinene, (–)- β -pinene, α -terpinene, γ -terpinene and terpinolene (and perhaps thymol), phenylpropenes safrole and eugenol, and the sulfur-containing compound diallyl disulfide have potent larvicidal action on one or more species of mosquitoes. Further studies are needed to show the robustness or limitations of these substances as single component mosquito larvicides. Also, further studies on combinations of these components are needed to explore possible synergism, especially in those cases where the EOs are more active than the individual, isolated components.

In what is apparently the first general demonstration that piperonyl butoxide (PBO) has synergistic effects on larvicidal monoterpenes and other classes of substances found in plant essential oils, Waliwitiya et al. [87] showed that synergism ratios of up to 250 (2.5 orders of magnitude) could be obtained for substances such as borneol, linalool, camphor, and 1,8-cineole, as summarized in Table 3. Importantly, 10 mg/L of piperonyl butoxide (PBO) was established as the minimum sublethal concentration in 1st through 4th instars of *Ae. aegypti*, and this (low) concentration was used in that study to guarantee that the observed enlarged effectiveness by PBO was synergistic in nature [87].

PBO is a synthetic synergist which is used in commercial applications together with pyrethroids and other contact insecticides. It is an insect monooxygenase inhibitor which reduces or eliminates the insect's capacity to detoxify larvicidal and adulticidal compounds [87].

Sandflies

Lutzomyia longipalpis Lutz & Neiva adults (sandfly vector of American visceral leishmaniasis) were killed by water extracts of the leaves of *Antonia ovata* Pohl ($LD_{50} = 233$ mg/mL) and water extracts of the roots of *Derris amazonica* Killip ($LD_{50} = 212$ mg/mL) [92]. Also, *Eucalyptus* spp. EOs exhibit toxic effects in contact with *L. longipalpis* adults. Thus, adulticidal effects were observed for lemon ironbark (*E. staigeriana* F. Muell. ex F.M. Bailey) EO (major components: limonene, *Z*-citral, α -citral), lemon eucalyptus (*E. citriodora* Hook.) EO (major component: β -citronellal), and eucalyptus (*E. globulus* Labill.) EO (major component: 1,8-cineole) ($EC_{50} = 0.59$, 5.04 , and 7.78 mg EO/mL, respectively). The superior toxicity of lemon ironbark is evident from these and other data and is due presumably to the activity of (major) components of its EO, which were not individually evaluated for biological activity [93].

In the above study, *Eucalyptus* spp. EOs were also shown to exhibit toxic effects by spraying directly onto *L. longipalpis* larvae. Thus, larvicidal effects were observed for *E. staigeriana*,

Table 2 Median lethal concentrations (LC₅₀) for volatile components of essential oils against larvae of mosquito species. Unless specified otherwise, all LC₅₀ values refer to a 24 h period of exposure. All LC₅₀ values are in ppm.

| Volatile component | <i>Ae. aegypti</i> | | | | <i>Ae. albopictus</i> | | | | | <i>Cx. pipiens</i> biotype <i>molestus</i> | <i>Cx. pipiens pallens</i> | <i>Oc. caspius</i> | <i>Oc. togoi</i> | Misc. |
|--------------------------|--------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|-------------------|-----------|--|----------------------------|--------------------|------------------|----------------------------|
| | [77] | [79] | [80] | [81] | [78] | [81] | [80] | [79] | [82] | [86] | [77] | [85] | [77] | |
| <i>Trans</i> -anethole | | | | | | | | | 24/48 h | 48 h | | 74.0/76.8 | | |
| β -Asarone | 27.0 | | | | | | | | | | 22.4 | | 26.4 | |
| Benzaldehyde | | | | | | | | | 47.0/45.4 | | | | | |
| Borneol | 94.9 | | | | | | | | | | 91.6 | | 97.3 | |
| γ -Cadinol | | | | | | | | | 92.7/74.5 | | | | | |
| Camphene | 67.0 | | | | | | | | | | 70.5 | | 68.7 | |
| 3-Carene | 19.2 | 27.9 | 25.3 | | | 24.1 | 22.9 | | | | 13.8 | | 16.2 | |
| Carvacrol | | | | | 70 | | | | | | | 35.5/34.6 | | |
| β -Caryophyllene | 88.3 | | | | | | | | | | 93.7 | | 97.9 | |
| Caryophyllene oxide | | | | | 125 | | | | 65.6/58.3 | | | | | |
| 1,8-cineole | 74.9 | | | | | | | | | | 79.0 | | 83.2 | |
| <i>E</i> -Cinnamaldehyde | | | | | | | | | 48.1/47.4 | | | | | 37.5/ 18.3 ^f |
| Cinnamyl acetate | | | | | | | | | 52.7/45.0 | | | | | |
| Citral | | | | | | | | | 70.7/65.4 | | | | | |
| <i>p</i> -Cymene | | 43.3 | 37.1 | 19.2 | | 46.7 | 25.9 | 34.9 | | | | | | |
| Diallyl disulfide | | | | | | | | | | | | | | 6.61 ^d |
| 3,5-Dimethoxytoluene | 64.1 | | | | | | | | | | 55.1 | | 67.0 | |
| Estragole | 46.4 | | | | | | | | | | 54.0 | | 58.5 | |
| Eugenol | | | | | | | | | 67.4/54.8 | | | 7.53/5.57 | | |
| Fenchene | 69.3 | | | | | | | | | | 72.2 | | 95.2 | |
| 16-Kaurene | | | 57.0 | | | | 56.5 | | | | | | | |
| (+)-Limonene | 24.5 | 19.4 ^b | | 18.1 ^b | 37 | 32.7 ^b | | 15.0 ^b | | | 13.3 | | 19.2 | |
| Linalool | 96.6 | | | | | | | | | | 94.8 | | 99.0 | |
| Linalyl acetate | | | | | | | | | | | | | | 23.1 ^e |
| Methyleugenol | 57.7 | | | | | | | | | | 53.3 | | 58.5 | |
| Myrcene | 66.4 | 27.9 ^a | 35.8 ^a | | | 27.0 ^a | 23.5 ^a | | | | 66.3 | | 64.8 | |
| Myristicin | 73.0 | | | | | | | | | | 77.0 | | 90.7 | |
| Pentadecane | 96.7 | | | | | | | | | | 97.6 | | 99.2 | |
| α -Phellandrene | 23.1 | | | 16.6 | | 39.9 | | | | | 13.8 | | 16.1 | |
| (+)- α -Pinene | 50.9 | | | | | | | | | 61.5 | 54.0 | | 47.3 | |
| (-)- α -Pinene | 64.8 | | 79.1 ^c | | | 74.0 ^c | | | | 58.4 | 70.4 | | 57.9 | |
| (+)- β -Pinene | 22.4 | | | | | | | | | 66.5 | 21.1 | | 25.6 | |
| (-)- β -Pinene | 15.4 | | | | | | | | | 36.5 | 12.9 | | 18.0 | |
| Safrole | 9.88 | | | | | | | | | | 8.22 | | 16.1 | |
| Terpinen-4-ol | 64.8 | | | | | | | | | | 58.3 | | 58.5 | |
| α -Terpinene | | | 28.1 | 14.7 | | 25.2 | 22.4 | | | | | | | |
| γ -Terpinene | 17.1 | 26.8 | 26.8 | 30.7 | 95 | 29.8 | 22.8 | 22.8 | | | 12.6 | | 14.4 | |
| Terpinolene | 15.3 | | 32.1 | 28.4 | | 35.6 | 22.0 | 21.3 | | | 11.9 | | 14.2 | |
| Thymol | | | | | 79 | | | | | | | 33.7/33.3 | | |
| 3,4,5-Trimethoxytoluene | 67.1 | | | | | | | | | | 74.8 | | 91.4 | |
| Verbenone | 93.2 | | | | | | | | | | 96.0 | | 90.6 | |

^a β -myrcene was the compound mentioned; ^b limonene was the compound mentioned; ^c α -pinene was the compound mentioned. ^d *Cx. pipiens* third and fourth instars, 48 h LC₅₀ mg/L from *Allium sativum* [83]. ^e *Cx. pipiens* biotype *molestus* larvae, LC₅₀ mg/L from *Citrus × aurantium* [84]. ^f *Cx. quinquefasciatus* fourth instars, 24/48 h LC₅₀ mg/L from *Cinnamomum osmophloeum* [82]

E. citriodora, and *E. globulus* EOs (EC₅₀ = 2.63, 1.78, and 25.3 mg EO/mL, respectively) [93].

Dry, powdered, and otherwise unprocessed fruit and leaves of the broad-spectrum insectidal plants *A. indica* and *Melia azedarach* L. were tested in a no-choice feeding experiment against *L. longipalpis* first instars which were allowed to develop over a period of 30 days. All 4 types of extract had significant larvicidal effects as compared to controls fed an untreated, normal diet.

A. indica fruit extracts totally prevented third instars from moulting, thus resulting in no fourth instars. Feeding *M. azedarach* fruit totally prevented fourth instars of *L. longipalpis* from moulting (100% mortality) while feeding leaves of *M. azedarach* totally prevented moulting of second instars (100% mortality) [91]. Also, direct spraying of *Eucalyptus* spp. EOs onto *L. longipalpis* eggs produced ovicidal effects. Thus, *E. staigeriana*, *E. citriodora*,

Table 3 Larvicidal activity of selected monoterpenoids and *trans*-anethole with and without piperonyl butoxide (PBO) to first- through fourth-instars of *Aedes aegypti* exposed for 24 h. All values are means of n = 3 experiments [87].

| Chemical | Range of lethality to 1st–4th instars | | |
|------------------------|---------------------------------------|-----------------------|---------------------------|
| | without PBO | with PBO | Range of Synergism Ratios |
| | LC ₅₀ mg/L | LC ₅₀ mg/L | SR _{1–4} |
| <i>Trans</i> -anethole | 13–88.5 | 2.6–25.3 | 4–17 |
| Borneol | 183–>500 | 2.0–24.6 | 20–250 |
| Borneol acetate | >500 | 3.0–39.3 | 13–167 |
| Camphor | >500 | 2.1–71.8 | 7–238 |
| 1,8-Cineole | >500 | 2.1–96.2 | 5–238 |
| Citronellal | 40.7–263 | 2.9–15.6 | 14–37 |
| <i>p</i> -Cymene | 226–>500 | 5.2–23.2 | 22–44 |
| Eugenol | 24.5–143 | 2.3–52.3 | 3–11 |
| Linalool | >500 | 2.0–99.5 | 5–250 |
| α -Pinene | 82.3–>500 | 2.8–20.7 | 24–151 |
| β -Pinene | 96.2–>500 | 2.5–30.7 | 16–167 |
| Pulegone | 10.3–48.7 | 3.2–15.1 | 3–8 |
| Terpineol | 83.9–>500 | 3.2–8.5 | 26–128 |
| Thymol | 17.3–53.5 | 2.7–19.8 | 3–8 |

and *E. globulus* EOs are active mosquito ovicides (EC₅₀ = 3.60, 9.44, and 9.23 mg EO/mL, respectively) [93].

In a study performed in Ethiopia, *Phlebotomus bergeroti* Parrot adults (visceral leishmaniasis vector) were repelled by *A. indica* (neem) oil as 2 and 5% solutions in coconut oil providing 96.3% protection (for up to a mean time of 440 min) and 98.3% protection (for up to 9 h), respectively, under lab conditions. Also, *P. bergeroti* adults were repelled by *M. azedarach* (chinaberry) oil in 2 and 5% formulations in coconut oil which provided 95.1% protection (for 440 min) and 96.2% protection (for 500 min), respectively, under lab conditions. In tests against field populations of *Phlebotomus orientalis* Parrot and *P. bergeroti*, 2 and 5% neem oil in coconut oil mixtures and DEET provided more than 95% protection against *P. orientalis* for mean times of 8 h 24–48 min. Inter-

estingly, pure coconut oil also provided good protection (86%) against *P. orientalis* (no significant difference compared to test oil solutions and DEET) and providing a protection time of 504 min. Two concentrations of neem oil solution and pure coconut oil provided >92% protection for 480–576 min against *P. bergeroti*. DEET provided a lower mean protection of 76% against *P. bergeroti* for about 528 min (though this was not significantly different than test solution and coconut oil results). These results provide evidence for the value of both neem and coconut oils in the field as effective repellents to *Phlebotomus* Rondani & Berté spp. [94]. In other work, *P. papatasi* Scopoli mature females were repelled by garlic clove (*Allium sativum*) oil (1 and 0.005% oil exhibited 97 and 49% repellency, respectively) [95].

Scabies mites

“Itch mite”, *Sarcoptes scabiei* var *hominis* Hering, is the arthropod agent of human scabies, a debilitating skin disease. The median lethal time (LT₅₀) for *Sarcoptes scabiei* Linnaeus [96] treated with a 10% neem (*A. indica*) oil microemulsion was 81.7 min; with a 10% neem oil aqueous emulsion, 95.6 min; and with a microemulsion without neem oil, 89.1 min. The effectiveness of the microemulsion without neem oil is due to sodium dodecyl benzene sulfonate (SDBS) in the formulation which is known to have acaricidal activity in other studies [96]. Also, from the chloroform extracts of *A. indica* (neem) oil the acaricidal substance octadecanoic acid-tetrahydrofuran-3,4-diyl ester (24 h LC₅₀ = 0.1 mg/mL; LT₅₀ = 15.3 h at a concentration of 7.5 mg/mL) was isolated [97]. In other work, EOs and their components were screened for activity against permethrin-resistant (*S. scabiei* var *canis* Gerlach mites harvested from rabbits) and permethrin-sensitive (*S. scabiei* var *suis* Gerlach mites harvested from pigs) scabies mites, and active samples which were: clove EO (EC₁₀₀ ≥ 6.25% EO and 1.56% EO, respectively; mean survival time = 0.25 h), eugenol (EC₅₀ = 13.0 and 40.7 mM, respectively), isoeugenol (EC₅₀ = 24.6 and 32.1 mM, respectively), acetyleugenol (EC₅₀ = 19.4 and 30.8 mM, respectively), benzyl benzoate (positive control, EC₅₀ = 24.5 and 27.2 mM, respectively). Derivatives of eugenol and eugenol-rich clove EO show potential for use in the treatment of resistant and sensitive scabies mites [98].

Table 4 Median lethal and knockdown data (fumigant activity) for chemical components of EOs against adult mosquitoes.

| Chemical component | <i>Ae. aegypti</i> | | Female [90] | | <i>An. gambiae</i> | | <i>An. tessellatus</i> | | <i>Cx. quinquefasciatus</i> | | |
|------------------------|-----------------------|-----------------------|------------------|------------------|--------------------|--|------------------------|------------------|-----------------------------|------------------|------------------|
| | Male & female | | | | Male & female | | Male & female | | Male & female | Female | |
| | LD ₅₀ [88] | KT ₅₀ [89] | KD ₅₀ | LC ₅₀ | LD ₅₀ | | KD ₅₀ | LC ₅₀ | LD ₅₀ | KD ₅₀ | LC ₅₀ |
| β -Caryophyllene | | | | | | | 1.1 | 0.80 | | 2.2 | 5.3 |
| 1,8-Cineole | | 3.90 | | | | | | | | | |
| <i>p</i> -Cymene | | 5.82 | | | | | | | | | |
| Geijerene | 6.8 | | | | 4.2 | | | | 5.4 | | |
| Germacrene D | 2.8 | | | | 1.8 | | | | 2.1 | | |
| L-Menthol | | | | | | | 0.54 | 0.36 | | 0.50 | 0.50 |
| Mugetanol | | | 0.36 | 0.80 | | | 0.31 | 0.55 | | 0.17 | 0.17 |
| α -Pinene | | 5.36 | | | | | | | | | |
| Pregeijerene | 5.1 | | | | 3.0 | | | | 3.9 | | |
| Pulegone | | | 3.3 | 5.3 | | | 0.84 | 1.33 | | 1.62 | 3.31 |
| γ -Terpinene | | 9.31 | | | | | | | | | |
| 4-Terpineol | | 9.27 | | | | | | | | | |
| α -Terpineol | | | 0.75 | 0.62 | | | 0.59 | 0.45 | | 0.59 | 0.56 |
| Thymol | | | 0.49 | 0.66 | | | 0.38 | 0.51 | | 0.60 | 0.71 |

LD₅₀ – median lethal dose; KD₅₀ – median knockdown dose; KT₅₀ – median knockdown time; LC₅₀ – median lethal concentration. LD₅₀, KD₅₀, and LC₅₀ in μ g/mL, KT₅₀ in min

Ticks

Plant EOs and components exhibit significant adulticidal activities against ticks. Java citronella (*Cymbopogon winterianus* Jowitt ex Bor) EO exhibited lethal effects against *Rhipicephalus (Boophilus) microplus* Canestrini engorged females ($DL_{50} = 6.1\%$ EO) [109]. Furthermore, *C. winterianus* EO can be sprayed or poured onto feeding ticks and causes a 45–75% reduction 22–28 days after treatment began [110]. The major components of *C. winterianus* were each tested against *R. microplus* and exhibited LC_{50} of 21.0% for citronellal and 17.8% for geraniol against blood-engorged females, and citronellol was much less toxic ($LC_{50} = 78.9\%$) [110]. In other work, the EO (contains carvacrol) of the aerial parts of *Origanum minutiflorum* O. Schwarz & P.H. Davis is lethal to *R. turanicus* Pomerantsev adults, and 10 μ L EO/L causes 100% death in 120 min [111]. In another study, the EO of the aerial parts of *Lavandula angustifolia* exhibited toxicity to blood-engorged female *R. annulatus* ($LC_{50}/LC_{99} = 2.76/8.84\%$ EO) [112].

The bioactive compound azadirachtin present in *A. indica* (neem) fruit and kernel extracts affects tick embryo development and molting stages. Interestingly, sheep (*Ovis aries* L.) which consumed a feed containing *A. indica* fruit and kernel extracts exhibited no noticeable signs of toxicity. This diet negatively affected the ability of the American dog tick *Dermacentor variabilis* Say to feed on sheep blood which exhibited plasma levels of azadirachtin of 4.35–4.81 μ g/mL over 14 days [113]. Sheep which consumed feed containing 0.6% azadirachtin had ticks which weighed ca. half as much as the ones from sheep which did not consume the *A. indica* extract. Azadirachtin in blood plasma impaired blood feeding by ticks, and so *A. indica* extracts as food additives may have applications in tick control for use in public health and veterinary applications [113].

Plant EOs and component chemicals exhibit significant larvicidal activities against ticks. In the larvae immersion test, *Hesperozygis ringens* (Benth.) Epling EO (86% pulegone) was lethal to *R. microplus* ($LC_{99.9} = 0.541 \mu$ L/mL, $LC_{50} = 0.260 \mu$ L/mL) as was pulegone ($LC_{99.9} = 0.602 \mu$ L/mL, $LC_{50} = 0.321 \mu$ L/mL) [106]. *C. winterianus* EO had lethal effects on *R. microplus* larvae ($DL_{50} = 4.1\%$ EO) [109]. Plant EOs and components deter oviposition by ticks. For example, 5% geranium (*Pelargonium roseum* Willd.) leaf and stem EO and 100% *Cymbopogon nardus* (L.) Rendle leaf EO exhibited 88 and 100% oviposition deterrent effects on *R. annulatus* Say blood-engorged females [107, 108]. Also, *C. winterianus* EO exhibited total oviposition deterrence ($EC_{100} = 10\%$ EO) [109], and at a concentration of 20%, *C. winterianus* EO exhibited total oviposition deterrence in *R. microplus* blood-engorged females [110].

Plant EOs and component chemicals exhibit anti-hatching activity against ticks. *Hesperozygis ringens* (Benth.) Epling EO (86% pulegone) was tested at concentrations of 25 and 50 μ L/mL in the adult immersion test and exhibited inhibitions of 48 and 76%, respectively, in egg production by *R. microplus* blood-engorged females as compared to controls. The eggs which were produced by these treated females exhibited infertility (30–95% anti-hatching activity). Pure pulegone gave the same results as EO in the above tests [106]. Furthermore, *C. nardus* EO had 100% anti-hatching activity against *R. annulatus* [108]. Similarly, *C. winterianus* EO exhibited total anti-hatching activity on *R. annulatus* eggs ($EC_{100} = 7.1\%$ EO) [109]. The major chemical components of *C. winterianus* were each tested against *R. microplus*, and 50% citronellal and 25% geraniol caused 100% sterility of eggs (no hatching) [110]. In another study, the EO of the aerial parts of *L. angustifolia* was tested against *R. annulatus* blood-engorged females. At

4.0% EO, female *R. annulatus* suffered a 100% failure to produce eggs and $\geq 6\%$ EO provided 100% egg laying failure [112].

Several recent applications of plant extracts and isolated natural compounds as tick repellents have been described in the scientific literature. In the wrapped finger assay, the ethanol extracts of the aerial parts of *C.nardus* ($EC_{50} = 0.089 \text{ mg/cm}^2$), the leaves of *Ageratum conyzoides* ($EC_{50} = 0.205 \text{ mg/cm}^2$), and the isolated natural compound callicarpinal ($EC_{50} = 0.084 \text{ mg/cm}^2$) (from the leaves of *Callicarpa americana* L.) all exhibited significant repellent effects against the dog tick *Amblyomma cajennense* Fabricius [99]. Also, the gum resin (composed of germacrene D, δ -elemene, β -bourbonene) of *Commiphora holtziana* Engl. provided over 5 h of repellent protection against *R. microplus* adults [100]. In other work, *Ixodes ricinus* L. nymphs were repelled by the toluene extracts of the twigs and leaves of *Artemisia abrotanum* L. (57% repellency after 8 h) and by the active chemical components thujyl alcohol, eugenol, and coumarin (83, 98, and 98% repellency, respectively, after 8 h) [101].

Chemical components of plant EOs are a very interesting group of substances having confirmed efficacy in tick control. For example, *Ixodes ricinus* nymphs are repelled by carnation (*Dianthus caryophyllus* L.) EO (92% repellency after 8 h). The active components present in *D. caryophyllus* flower EO were 2-phenylethanol, β -citronellol, cinnamyl alcohol, geraniol, and α -pinene which when tested individually exhibited 96, 84, 80, 79, and 75% repellency, respectively, against *I. ricinus* after 8 h [101].

Undecanone is a valuable tick repellent which originally derived from the wild tomato plant, *Lycopersicon hirsutum* fo. *glabratum* C.H. Mull. In assays involving treated vs. untreated cotton cheesecloth and direct comparison, a 7.75% 2-undecanone commercial formulation exhibited mean percentage repellency against the lone star tick *Amblyomma americanum* L. and *D. variabilis* which was greater than or comparable in efficacy to arthropod repellent products containing 98.1% N,N-diethyl-m-toluamide (DEET), 19.6% IR3535, and 30% lemon eucalyptus (*Eucalyptus citriodora*) EO. Products containing 5% and 15% picaridin and 0.5% permethrin were less repellent than the 7.75% 2-undecanone formulation [102]. The high repellency of a commercial formulation containing 7.75% 2-undecanone as the active ingredient against *D. variabilis* and blacklegged tick *Ixodes scapularis* Say was confirmed in other work [103].

Brown ear tick *Rhipicephalus appendiculatus* Neumann adult climbing is repelled by the EO of *Commiphora swynnertonii* Burt, and a 0.1% solution of α -copaene provided 86% repellency while a 1% solution had repellency comparable to DEET. Isocaryophyllene also exhibited repellent activity against adult *R. appendiculatus* (10% solution, 55% repellency) [100].

In other work, *Amyris balsamifera* L. EO ($EC_{50} = 9.0$ and 22.9μ g/cm², respectively) and elemol ($EC_{50} = 10.9$ and 14.8 nmol/cm^2 , respectively), a major chemical constituent of the EO of osage orange [*Maclura pomifera* (Raf.) C.K. Schneid.], effectively repelled *A. americanum* host-seeking nymphs in climbing filter paper and wrapped fingertip assays, and elemol exhibited comparable repellency to DEET. Elemol and amyris EO also effectively repelled *I. scapularis* ($EC_{50} = 5.16$ and 4.20μ g/cm², respectively, in the wrapped fingertip assay) [104]. A common component of plant EOs, geraniol, in mixtures containing cinnamon (*Cinnamomum* Schaeff. sp.), lemongrass (*Cymbopogon citratus* (DC.) Stapf), rosemary (*Rosmarinus officinalis* L.), wintergreen (*Gaultheria procumbens* L.), and canola oils as topical repellents exhibits longevity and repellency comparable to or better than DEET against *D. variabilis* and *I. scapularis* [105].

Conclusion

Much information has been made available in the past few years on active plant extracts, fractions, EOs, and their isolated components which are responsible for lethal effects against arthropods. Plant extracts or chemicals which owe their origins to plants such as *A. indica* (neem) oils and other derivatives, azadirachtin, undecanone, among others already have important commercial applications in a variety of commercial products which are useful for arthropod control. It is of major importance for future work that more importance be given to two general areas of research. One area involves the probable differences in enantiomeric purity of EO components which are purchased and used in bioassays to confirm the active anti-arthropod activity in many of the references cited and the enantiomeric purity of said component in the active EO. In future work involving chiral monoterpenes, the enantiomeric purity of the active component in the EO and in the purchased reference sample should be taken into account. Another area of importance is the deciphering of the synergistic, suppressive, and other interactions of the components of EOs (and extracts) as was done in the complex and stimulating work by Yoon et al. [33] for the components of *Citrus* L. EOs against several cockroach species. In many of the scientific papers reviewed herein, the isolated active components are recognizably less active than the plant extracts and EOs from which they were isolated, and so doubt remains whether the component is the most important active component or whether synergism or perhaps a "cocktail of components" is in fact the active agent responsible for the effect of the plant derivative. For many arthropod vectors, besides phytochemicals which are already found in commercial products, there are at least a few promising botanical candidates for control or development of control products in the future.

Supporting information

In Supporting Information, URLs of documents on human diseases borne by arthropod vectors, data from literature sources on plant extracts, EOs, monoterpenes, and phenylpropanoids exhibiting fumigant and other activities against *M. domestica* and extracts, EOs and fractions exhibiting lethal effects to mosquitoes are presented.

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