A Review of Resistance Mechanisms of Synthetic Insecticides and Botanicals, Phytochemicals, and Essential Oils as Alternative Larvicidal Agents Against Mosquitoes

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Mosquitoes are a serious threat to the society, acting as vector to several dreadful diseases. Mosquito management programs profoundly depend on the routine of chemical insecticides that subsequently lead to the expansion of resistance midst the vectors, along with other problems such as environmental pollution, bio magnification, and adversely affecting the quality of public and animal health, worldwide. The worldwide risk of insect vector transmitted diseases, with their associated illness and mortality, emphasizes the need for effective mosquitocides. Hence there is an immediate necessity to develop new eco-friendly pesticides. As a result, numerous investigators have worked on the development of eco-friendly effective mosquitocidal compounds of plant origin. These products have a cumulative advantage of being cost-effective, environmentally benign, biodegradable, and safe to non-target organisms. This review aims at describing the current state of research on behavioral, physiological, and biochemical effects of plant derived compounds with larvicidal effects on mosquitoes. The mode of physiological and biochemical action of known compounds derived from various plant families as well as the potential of plant secondary metabolites, plant extracts, and also the essential oils (EO), as mosquitocidal agents are discussed. This review clearly indicates that the application of vegetal-based compounds as mosquito control proxies can serve as alternative biocontrol methods in mosquito management programs.

Keywords: biopesticide, vector, secondary metabolites, phytochemical, physiology, enzyme, toxicity

INTRODUCTION

Vector borne diseases account for more than seven million deaths annually (World Health Organization [WHO], 2017), among which mosquito borne diseases are the most threatening due to their wide spread occurrence, consequently featuring a higher frequency of disease transmission (Lounibos, 2002; Tyagi et al., 2015). Among different mosquito families, Culicidae is a large family...
(3,300 Service species-41 genera) comprising *Toxorhynchitinae*, *Anopheinae* (anophelines), and also *Culicinae* (culcines) sub-families (Service, 1996; Senthil-Nathan et al., 2005b). Among the 31 genera, *Anopheles*, *Culex*, and *Aedes* are the most detrimental. *Anopheles* species, are carriers of major life-threatening diseases (malaria and filariasis-transmitting agents, such as *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*) and also of a few arboviruses (Kalaivani et al., 2012; Benelli et al., 2018; Thanigaivel et al., 2019; Vasantha-Srinivasan et al., 2019).

The discovery of DDT’s insecticidal properties in late 1930s/beginning of 1940s and the following progress of organochlorine invention and organophosphate insecticides concealed biological pesticide merchandise-research since the responses to mosquito regulation were supposed to have remained established (Shaalan et al., 2005; Senthil-Nathan et al., 2006a,b). The ranges of many of the mosquito species were not limited and keep expanding, thereby up surging the rates of disease incidence. Until recently, the use of several of the earlier synthetic-insecticides, such as permethrin and malathion, along with other organophosphates in vector control programs has been partial. This is due to absence of unique-insecticides, expense of synthetic-insecticides, apprehension for ecological sustainability, damaging influence on human health, besides further non-target populations, their persistent nature, greater amount of “biological magnification” through ecosystem and also the development of insecticide resistance (Ghosh et al., 2012). The emergence of DDT resistance in *Aedes* species (*Ae. tritaeniorhynchus* and *Ae. sollicitans*) lead to numerous drawbacks in mosquito control programs (Brown, 1986). Several categories of Mosquitocides are being implemented in malaria control programs (BHC, organophosphorus, carbamate, and pyrethroid). The ability of mosquitoes to evade the insecticidal action of these synthetic compounds are attributed to the increase in the rate of synthesis of detoxifying enzymes such as monoxygenases (MFOs), glutathione-S-transferases (GST) and carboxy-cholinesterase (CCE). MFOs are often associated with metabolic resistance to pyrethroids, such as permethrin, while GSTs are usually associated with organochloride resistance such as DDT. Resistance to pyrethroids, organophosphates and carbamates, such as bendiocarb are incurred by the magnification of CCE activity (Hemingway and Ranson, 2000). Added insecticides, benzophenyl urea and the larvicide, *Bacillus thuringiensis israelensis* (Bti), have partial use against mosquitoes. Unpredicted natural or anthropogenic associated ecological variations that modify the original habitats severely affect the vector biology thereby positively influencing their existence and disease incidence, thus constraining the frame-work of mosquito control strategies.

### BIOLOGICAL MANAGEMENT OF MOSQUITOES

Several phytochemicals from several plant families are identified with larvicidal activities against different mosquito species (*Table 1*). Plant extracts with their augmented phytochemical elements have a recognized potential as a substitute to conventional mosquito control agents (Sukumar et al., 1991; Tripathi et al., 2009; Tehri and Singh, 2015). The main strategy for mosquito control deals with the restriction of the vector population. As a promising biocontrol agent, the compounds from the plants of the family *Meliaceae* such as neem *Azadirachta indica* A. Juss (Senthil-Nathan et al., 2005b; Senthil-Nathan, 2013), Indian white cedar, *Dysoxylum malabaricum* Bedd. (Senthil-Nathan et al., 2006a), *D. beddomei* and chinaberry tree, *Melia azedarach* L. (Senthil-Nathan et al., 2006b) were effective against *An. stephensi* (Senthil-Nathan et al., 2008).

“Secondary metabolites” from *Eucalyptus tereticornis* Sm. (forest red gum, *Myrtaceae*) exhibited effective mosquitocidal activities against *An. stephensi* as reported by Senthil-Nathan (2007). Also, the crude metabolic extracts of *Acanthospermum hispidum* leaves were active against *An. stephensi*, *Ae. Aegypti*, as well as *Cx. quinquefasciatus* as reported by Vivekanandhan et al. (2018a,b). A study conducted on testing the mosquitocidal activity of *Justicia adhatoda* L. (*Acanthaceae*) leaf extracts revealed the potential of natural larvicidal agent against *Ae. Aegypti* (Thanigaivel et al., 2012, 2017a,b).

Besides secondary metabolites, essential oils (EOs) from plants were also recorded with effective mosquitocidal potentials. The EOs from the plants of *Lamiaceae* and *Zingiberaceae* were proved with bioactivity against *Ae. aegypti* (Kalaivani et al., 2012). The fern *Actiniopteris radiata* was tested with novel mosquitocidal activity against larvae of *Ae. aegypti* and *An. Stephensi* (Kamaraj et al., 2018). The seed oil extract of *Acacia nilotica* possessed robust larvicidal action against major mosquito vectors (Vivekanandhan et al., 2018a). A remarkable biological activity of EOs against Dengue vectors has been extensively reviewed by Chellappandian et al. (2017, 2018, 2019). Plant volatile oils were also conveyed with mosquitocidal potentials. As studied by Vasantha-Srinivasan et al. (2018), the crude volatile oil (CVO) from Piper beetle leaves possessed significant larvicidal, ovipositional, and repellency effects against *Ae. Aegypti*.

Derivatives of plants are enriched with active molecules with exceptional mosquitocidal properties and can be advanced as low cost environmentally friendly bio-pesticides. Many botanical extracts along with their chief constituents showed effective insect metabolism inhibition or stimulation of digestive enzymes (Senthil-Nathan et al., 2009; Napoléao et al., 2012; Senthil-Nathan, 2013). Unlike synthetic chemicals, previous literature on plant compounds doesn’t provide any indication for the emergence of resistance so far. This is most likely due to the blend of several bioactive compounds with different mechanisms of action and therefore it is difficult for mosquito vectors to develop resistance (Mulla and Su, 1999; Shaalan et al., 2005).

### IMPACT OF PHYTOCHEMICALS ON THE PHYSIOLOGY OF MOSQUITO Larvae

As in general, plant secondary metabolites are evolved as protection mechanism against herbivory. When these toxic substances are encountered by the mosquitoes, a relatively unambiguous response is triggered that has a non-specific influence on a wide range of molecular targets such as...
| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|-------------------|-----------------|------------|
| **Acanthaceae**          |                   |                 |            |
| Andrographis paniculata  | Andrographolide   | Aedes aegypti   | Edwin et al., 2016 |
| **Alangiaceae**          |                   |                 |            |
| Alangium salvifolium     | Asarinin, sesamin and (+)-xanthoxyloy-γ,γ-dimethylallylether, Hexadeccanoic acid, 1 hydroxymethyl-1,2-ethanediyl ester | Aedes aegypti | Thanigaivel et al., 2017a |
| **Amaranthaceae**        |                   |                 |            |
| Chenopodium ambrosioides | α-Terpineol       | Aedes aegypti   | Leyva et al., 2009b |
| **Amaryllidaceae**       |                   |                 |            |
| Alium macrostemon        | Methyl propyl disulfide; mimethyl trisulfide | Aedes albopictus | Liu et al., 2014a |
| Alium monanthum          | Dimethyl trisulfide; dimethyl tetrasulfide | Aedes aegypti | Moon, 2011 |
| **Anacardiaceae**        |                   |                 |            |
| Pistacia terebinthus     | α-Pinene; cyclopentane | Culex quinquefasciatus | Cetin et al., 2011 |
| Spondias purpurea         | Caryophyllene oxide and α-cadinol | Aedes aegypti | Lima et al., 2011 |
| **Annonaceae**           |                   |                 |            |
| Cananga odorata          | Benzyl acetate, linalool, methyl benzoate | Aedes aegypti | Vera et al., 2014 |
| Guatteria blepharophylla | Caryophyllene oxide | Aedes aegypti | Aciole et al., 2011 |
| Guatteria fríeana        | β-Eudesmol        | Aedes aegypti   | Aciole et al., 2011 |
| Guatteria hispida        | β-Pinene and α-pinene | Aedes aegypti | Aciole et al., 2011 |
| Rollinia leptopetala     | Spathulenol        | Aedes aegypti   | Feitosa et al., 2009 |
| **Apiaceae**             |                   |                 |            |
| Angelica purpuraeofolia  | 4’-Chloro-4,4-dimethyl-3-(1-imidazolyl)-valerophenone, 1-Dodecanol, | Aedes aegypti | Nagella et al., 2012 |
| Anethum graveolens       | Limonene, carvone  | Aedes albopictus | Seo et al., 2015 |
| Apium graveolens         | R-+-Limonene       | Aedes aegypti   | Pitasawat et al., 2007 |
| Bupleurum fruticosum     | Limonene, carvone  | Aedes albopictus | Seo et al., 2015 |
| Carum carvi              | Carvone            | Aedes aegypti | Pitasawat et al., 2007 |
| Conopodium capillifolium | α-Pinene; β-pinene | Culex pipiens | Evergetis et al., 2009 |
| Coniandra sativum        | Linalool, 2,6-octadien-1-ol, 3,7- dimethyl-, acetate, E-β-cymene, β-pinene, cuminaldehyde | Aedes aegypti | Evergetis et al., 2009 |
| Cuminum cyminum          | trans-Anethole, Limonene | Aedes aegypti | Seo et al., 2015 |
| Daucus carota            | Carotol            | Aedes albopictus | Seo et al., 2015 |
| Elaeoselinum asclepium   | α-Pinene; sabinene | Aedes aegypti | Evergetis et al., 2009 |
| Foeniculum vulgare       | trans-Anethole, Limonene | Aedes aegypti | Rocha et al., 2015 |
| Heracleum pastinacifolium| Octyl acetate, Hexyl | Aedes aegypti | Tabanca et al., 2012a |
| Ligusticum chuanxiong    | octadecenoic acids | Aedes aegypti, Culex quinquefasciatus | Evergetis et al., 2009 |
| Oenanthe pimpinelloides  | γ-Terpine; α-cymene | Aedes aegypti | Pavela, 2015 |
| Pomponia anisum          | trans-anethole, α-Pinene; sabinene, β-phellandrene | Aedes aegypti | Pavela, 2016 |
| Petroselinum crispum     | β-phellandrene,myristicin, α & β-pinene, myrcene | Anopheles culicifacies | Evergetis et al., 2012 |
| Pe. Sativum              | Myristicin,1,8-cineole, 1,3,8-p-menthatriene | Aedes albopictus | Seo et al., 2015 |
| Trachyspermum ammi       | Thymol             | Aedes albopictus | Pandey et al., 2009 |
| **Apocynaceae**          |                   |                 |            |
| Cionura erecta L.        | Edren-9-one, alpha cadinol, eugenol and alpha muurolene | Anopheles stephensi | Mozaffari et al., 2014 |
| **Araliaceae**           |                   |                 |            |
| Dendropanax morbifera    | γ-Elemene          | Aedes aegypti   | Chung et al., 2009 |
| **Aristolochiaceae**     |                   |                 |            |
| Aristolochia indica      | Aristolochic acid I and II | Aedes aegypti | Pradeepa et al., 2015 |
| Asarum heterotropoides   | Methyleugenol and safrole | Aedes aegypti | Perumalsamy et al., 2009 |

(Continued)
| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|------------------|------------|
| **Asteraceae**           |                    |                  |            |
| Achillea millefolium     | Eucalyptol, β-pinene, borneol, sabine, camphene | Aedes albopictus | Conti et al., 2010 |
| Artemisia absinthium     | (Z)-β-ocimene, (E)-β-farnesene (Z)-en-yn-dicycloether | Aedes aegypti, Culex quinquefasciatus, Anopheles stephensi | Govindarajan and Benelli, 2016 |
| Ar. dracunculus          | Hexanal, isovaleric acid, (Z)-3-hexenol, Hexadecanod | Anopheles stephensi | Pour et al., 2016 |
| Artemisia vulgaris       | Camphor, Linalool, terpenen-4-ol, a-and b-thujone, b-pinene | Aedes aegypti | Bora and Sharma, 2011 |
| Ar. dracunculus          | Hexadecanol |                  |            |
| Artemisia vulgaris       | Myrcene, limonene, cineol | Aedes aegypti | Sujatha et al., 2013 |
| Ar. dracunculus          | Capillin | Aedes aegypti, Aedes albopictus | Bora and Sharma, 2011 |
| Blumea densiflora        | Borneol, germacrene D, β-caryophyllene, γ-terpinene, α-pinene | Anopheles anthropophagus | Zhu and Tian, 2011 |
| Artemisia vulgaris       | α-pinene | Aedes aegypti | Wu et al., 2010 |
| Ar. dracunculus          | Capillin | Aedes aegypti | Senthilkumar et al., 2008 |
| Blumea densiflora        | Piperitone | Aedes aegypti | Marques et al., 2011 |
| Tagetes erecta           | trans-Anethole | Aedes aegypti | Ruiz et al., 2011 |
| Tagetes minuta           | Methyl chavicol | Aedes aegypti | Vera et al., 2014 |
| Tagetes patula           | SE-octimone | Aedes aegypti | Ruiz et al., 2011 |
| Chamaemelum nobile       | α-pinene; Limonene and terp | Aedes aegypti | Dharmagadda et al., 2005 |
| **Bignoniaceae**         |                    |                  |            |
| Cybistax antisyphilitica| quinone | Aedes aegypti | Rodrigues et al., 2005 |
| **Boraginaceae**         |                    |                  |            |
| Auxemma glazioviana      | α-Bisabolol, α-cadinol, and T-muurolool | Aedes aegypti | Costa et al., 2004 |
| Cordia curassavica       | Cordiaquinones J and K | Aedes aegypti | Ioset et al., 2000 |
| Cordia leucomallodios     | α-Pinene | Aedes aegypti | Santos et al., 2006 |
| **Cucurbitaceae**        |                    |                  |            |
| Bryonopsis laciosa       | Goniotothalamin | Culex pipiens | Kabir et al., 2003 |
| **Cupressaceae**         |                    |                  |            |
| Callitris glaucothylla   | Guaiol & citroenolic acid | Aedes aegypti | Shaalan et al., 2006 |
| Chamaecyparis formosensis| Myrtenol | Aedes aegypti | Chung et al., 2006 |
| Cryptomeria japonica     | 16-Kaurene and elemol | Aedes aegypti, Aedes albopictus | Cheng et al., 2012 |
| Cunninghamia konishii    | Cedrol, α-Pinene | Aedes aegypti | Cheng et al., 2013 |
| Cupressus arizonic var. glabra | α-Pinene & epi-zonarene | Aedes aegypti | Ali et al., 2013 |
| Cupressus arizonic var. | Limonene, umbellulone α-pinene | Anopheles stephensi | Sedlach et al., 2011 |
| Cupressus benthamii      | Limonene; umbellulone | Aedes albopictus | Giatropoulos et al., 2013 |
| Cupressus macrocarpa     | Sabinene; α-Pinene; terpenen-4-ol | Aedes albopictus | Giatropoulos et al., 2013 |
| Cupressus sempervirens   | α-Pinene; 3-3-carene | Aedes albopictus | Giatropoulos et al., 2013 |
| Cupressus torulosa       | α-Pinene; 3-3-carene | Aedes albopictus | Giatropoulos et al., 2013 |
| Chamaecyparis formosensis| Myrtenol; myrtenal | Aedes aegypti, Aedes aegypti | Kuo et al., 2007 |
| Chamaecyparis lawsoniana | Limonene; oplopanonyl acetate; beyerene | Aedes albopictus | Giatropoulos et al., 2013 |
| Juniperus communis ssp.  | α-Pinene; 3-3-carene | Culex pipiens | Vourlioti-Arapli, 2012 |
| Hemisphaericus           | α-Pinene; limonene | Culex pipiens | Vourlioti-Arapli, 2012 |

(Continued)
TABLE 1 | Continued

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|------------------|------------|
| Juniperus drupacea       | Sabinene; 4-methyl-1-1-methylethyl-3-cyclohexen-1-ol | Culex pipiens | Vourlioti-Arapi et al., 2012 |
| Juniperus foetidissima   | Myrcene; germacrene-D; α-Pinene | Culex pipiens | Vourlioti-Arapi et al., 2012 |
| Juniperus oxycedrus L. ssp. oxycedrus | α-pinene | Culex pipiens | Vourlioti-Arapi et al., 2012 |
| Juniperus oxycedrus L. subsp. Macrocarpa | α-Pinene; l-3-carene; β-phellandrene; α-terpinyl acetate | Aedes albopictus | Giatropoulos et al., 2013 |
| Tetracnitis articulate | α-Pinene; bornyl acetate | Aedes albopictus | Giatropoulos et al., 2013 |
| Dioncophyllaceae         | dioncophylline A | Anopheles stephensi | François et al., 1996 |
| Euphorbiaceae            | Methyl eugenol   | Aedes aegypti   | Morais et al., 2006 |
| Croton nepetaefolius     | Ascaridole & p-Cymene | Aedes aegypti | Torres et al., 2008 |
| Croton regelianus        | E-anethole, p-anisaldehyde | Aedes aegypti | Morais et al., 2006 |
| Fabaceae                 | β-caryophyllene  | Anopheles darling, Aedes aegypti | Trindade et al., 2013 |
| Hymenaea courbaril       | α-Copaene, spathulanol | Aedes aegypti | Aguiar et al., 2010 |
| Myroxylon pereirae       | Benzyl benzoate  | Aedes aegypti   | Yenesew et al., 2003 |
| Millettia dura           | Rotenoids, deguelin and tephrosin caryophyllene oxide; phenol,4-3,7-dimethyl-3-ethenylocta-1,6-dienyl caryophyllene | Culex quinquefasciatus | Dua et al., 2013 |
| Psoralea coryllifolia    | Citronellol     | Aedes aegypti   | Benelli et al., 2017 |
| Geraniaceae              | Culex quinquefasciatus | Culex quinquefasciatus | Cavalcanti et al., 2004 |
| Pelargonium graveolens   | Nerul; geranial | Culex quinquefasciatus | Cavalcanti et al., 2004 |
| Gramineae                | α-Pinene        | Aedes aegypti   | Cetin et al., 2011 |
| Cymbopogon citratus     | Thymol          | Culex pipiens | Govindarajan et al., 2013 |
| Hypericaceae             | Δ3-carene, 1,8-cineole, β-caryophyllene, bicyclogermacrene | Culex tritaeniorhynchus, Aedes albopictus, and Anopheles subpictus | Araújo et al., 2003 |
| Lamiaceae                | β-caryophyllene, bergamotene, and terpinolene | Aedes aegypti | Jaenson et al., 2006 |
| Hyptis martusii          | E-Methyl-cinnamate | Aedes aegypti | Kulkarni et al., 2013 |
| Hyptis suaveolens        | Carvone         | Aedes aegypti   | Kulkarni et al., 2013 |
| Lavandula gibsoni        | α-Terpinolen and thymol | Aedes aegypti, Anopheles stephensi | Kulkarni et al., 2013 |
| Lavandula stoechas       | Fenchone, 1,8-Cineole | Culex pipiens | Traboulsi et al., 2002 |
| Lippia organoides        | Carvacrol       | Aedes aegypti   | Mar et al., 2018 |
| Mentha longifolia        | Piperitone oxide oxid | Aedes aegypti | Paviola et al., 2014 |
| M. microphylla           | Piperitone, Pulegone, Piperitone oxide | Culex pipiens | Traboulsi et al., 2002 |
| M. spicata               | Carvone         | Aedes aegypti   | Govindarajan et al., 2012 |
| Nepeta cataria           | E.Z-Nepetalactone and Z,E-nepetalactone | Aedes aegypti | Zhu et al., 2006 |
| Ocimum americanum        | E-Methyl-cinnamate | Aedes aegypti | Cavalcanti et al., 2004 |
| Ocimum basilicum         | Linalool; methyl eugenol | Aedes aegypti | Govindarajan et al., 2013 |
| Ocimum gratissimum       | Eugenol         | Aedes aegypti   | Cavalcanti et al., 2004 |
| Ocimum sanctum           | Methyl eugenol  | Culex pipiens | Gbolade and Lockwood, 2008 |
| O. syringum              | Carvacrol, Thymol | Aedes aegypti | Traboulsi et al., 2002 |
| Penila frutescens        | oleic, S-limonene, perillaldehyde | Aedes aegypti | Pohl et al., 2011 |
| Plectranthus amboinicus  | Carvacrol       | Aedes aegypti   | Lima et al., 2011 |
| Plectranthus mollis      | Pterpine oxid, fenichone | Aedes aegypti | Kulkarni et al., 2013 |
| Pogostemon cablin        | Patchouli alcohol, Seysahelene, α-bulhesene, Norpatchoulenol | Aedes aegypti | Lima-Santos et al., 2019 |
| Pulegium vulgar           | Pulegone, carvone | Aedes albopictus | Pavela, 2015 |

(Continued)
| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|-----------------|------------|
| Rosmarinus officinalis   | 1,8-Cineole; camphor | Aedes aegypti   | Giatropoulos et al., 2018 |
| Satureja hortensis       | γ-Terpinene; carvacrol | Culex pipiens | Pavela, 2009 |
| Thymus capitatus (L.)    | Thymol, alpha-Amyrin, Carvacrol + beta- | Aedes aegypti | Mansour et al., 2000 |
| Hoffm. & Link            | Caryophyllene      | Culex pipiens | Pitarokili et al., 2011 |
| Thymus leucospermus      | p-Cymene           | Culex pipiens | Pavela, 2009 |
| Thymus saturoides        | Thymol; borneol    | Aedes albopictus| Pitarokili et al., 2011 |
| Thymus teucrioides       | p-Cymene; γ-terpinene; thymol | Aedes aegypti | Giatropoulos et al., 2018 |
| Thymus vulgaris          | p-Cymene, carvacrol, thymol | Culex pipiens | Niroumand et al., 2018 |
| Vitex agnus castus       | Trans-caryophyllene, 1,8 cineole | Aedes aegypti | Kannathasan et al., 2011 |
| Vitex trifolia           | Methyl-p-hydroxybenzoate | Aedes aegypti |           |

**Lauraceae**

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|-----------------|------------|
| Cinnamomum camphora      | 1,8-Cineole        | Anopheles sinensis| Zhang et al., 2018 |
| C. cassia                | Cinnamaldehyde     | Aedes aegypti   | Zhu et al., 2006 |
| C. impressicostatum      | Benzyl benzoate and α-phellandrene | Aedes aegypti | Jantan et al., 2005 |
| C. japonicum             | Benzyl benzoate    | Anopheles sinensis| Zhang et al., 2018 |
| C. osmophloeum           | Benzyl benzoate    | Aedes aegypti   | Jantan et al., 2005 |
| C. pubescens             | Benzyl benzoate    | Aedes aegypti   | Jantan et al., 2005 |
| C. rhynochryx                | Benzyl benzoate    | Aedes aegypti   | Jantan et al., 2005 |
| C. scortechini            | β-Phellandrene and linalool | Aedes aegypti | Jantan et al., 2005 |
| C. sintoc                | Safrole            | Aedes aegypti   | Jantan et al., 2005 |
| C. subavenium            | Eugenol            | Anopheles sinensis| Zhang et al., 2018 |
| Laurus nobilis           | 1,8-Cineole        | Aedes aegypti   | Jantan et al., 2005 |

**Magnoliaceae**

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|-----------------|------------|
| Magnolia salicifolia     | Trans-anethole, Methyl eugenol, isomethyl eugenol, Costunolide, lactone and parthenolide | Aedes aegypti | Kelm et al., 1997 |

**Malvaceae**

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|-----------------|------------|
| Abutilon indicum         | β-sitosterol       | Aedes aegypti, | Rahuman et al., 2008a |
| Azadirachtin, salannin, deacetylgedunin, gedunin, 17-hydroxyazadiradione and deacetylnimbir | | | |

**Meliaceae**

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|-----------------|------------|
| Azadirachta indica       | Saponins           | Anopheles stephensi, | Senthil-Nathan et al., 2005a |
| 23-O-methylnimocinolide  | | | |
| 6α-O-acetyl-7-deacetylnimocinol | Culex quinquefasciatus | Aedes aegypti | Ansari et al., 2005 |
| Nimocinolide; 7-O-deacetyl-23-O-methyl-7α-O-senecioylnimocinolide | | Aedes aegypti | Siddiqui et al., 1999 |
| desfurano-6α-hydroxyazadiradione | | | Banerji and Nigam, 1984 |
| 22,23-dihydroxynomocinol | | Aedes aegypti | Naqvi, 1987 |
| 1a-acetyl-3α-propionylvilsin | | Aedes aegypti | Siddiqui et al., 2002 |
| Mellaetraolenone | | Aedes aegypti | Siddiqui et al., 2003 |
| azadirachtin, salannin, deacetylgedunin, gedunin, 17-hydroxyazadiradione and deacetylnimbir | | Culex quinquefasciatus | Siddiqui et al., 2003 |

**Dysoxylum malabaricum**

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|-----------------|------------|
| D. beddomei | Caryophyllene epoxide | Aedes aegypti | Senthil-Nathan et al., 2009 |
| | cis-Caryophyllene | Aedes aegypti | Senthil-Nathan et al., 2009 |

(Continued)
TABLE 1 | Continued

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|--------------------|------------------|------------|
| Guarea humaitensis       | 1α,7α,11β-triacetoxy-4α-carbomethoxy- | Aedes aegypti    | Massebo et al., 2009 |
| G. scabra                | 1β,2α-(2-methylpropanoyloxy)-14β,15β-epoxyhavanesin | Aedes aegypti    | Koutsaviti et al., 2015 |
| Turraea floribunda       | 1α,11β-diacetoxy-4α-carbomethoxy-7α- | Aedes aegypti    | Lima et al., 2011 |
|                         | hydroxy-12α-(2-methylpropanoyloxy)-15β-oxohavanesin; 1α-acetyl-3α-propionylhavanesin | Culex pipiens    | Leyva et al., 2008 |
| Turraea wakefieldii      | 11β,12α-diacetoxyneotecleanin | Aedes aegypti    | Lucia et al., 2008 |
|                         | 11β,12α-diacetoxy-14β,15β-epoxyneotecleanin | Aedes aegypti    | Lucia et al., 2008 |
| Myrtaceae                |                    |                  |            |
| Eucalyptus benthamii     | α-Pinene           | Aedes aegypti    | Lucia et al., 2012 |
| E. botryoides            | p-Cymene, α-eudesmol, and 1,8-cineol | Aedes aegypti    | Lucia et al., 2012 |
| E. camaldulensis         | 1,8-Cineol, p-cymene and β-phellandrene | Aedes aegypti    | Lucia et al., 2008 |
| E. citiodora             | Citronellal; citronellol; α-humulene isopulegol | Aedes aegypti    | Vera et al., 2014 |
| E. dunnii                | 1,8-Cineol and γ-terpinene | Aedes aegypti    | Lucia et al., 2008 |
| E. fastigata             | p-Cymene           | Aedes aegypti    | Lucia et al., 2012 |
| E. globulus              | 1,8-Cineol         | Aedes aegypti Anopheles arabiensis | Lucia et al., 2007 |
| E. grandis               | α-Pinene           | Aedes aegypti    | Lucia et al., 2008 |
| E. Gunnii                | 1,8-Cineol and p-cymene | Aedes aegypti    | Lucia et al., 2012 |
| E. nobilis               | 1,8-Cineol         | Aedes aegypti    | Lucia et al., 2012 |
| E. radiata               | 1,8-Cineol         | Aedes aegypti    | Lucia et al., 2012 |
| E. robusta               | α-Pinene           | Aedes aegypti    | Lucia et al., 2012 |
| E. saligna               | 1,8-Cineol and p-cymene | Aedes aegypti    | Lucia et al., 2008 |
| E. tereticornis          | β-Phellandrene and 1,8-cineol | Aedes aegypti    | Lucia et al., 2008 |
| E. urrophylla            | 1,8-Cineol         | Aedes aegypti    | Cheng et al., 2009b |
| E. melanadenia           | 1,8-Cineol         | Aedes aegypti    | Aguilera et al., 2003 |
| Myrtus communis          | 1,8 Cineole, α-Pinene, Linalool | Culex quinquefasciatus | Traboulsi et al., 2002 |
| M. disstiflora           | Terpinen-4-ol      | Aedes aegypti    | Park et al., 2011 |
| M. leucadendron          | 1,8-Cineol, α-pinene, and α-terpinol | Aedes aegypti    | Leyva et al., 2008 |
| M. Laurencia             | Terpinem-4-ol and γ-terpinene | Aedes aegypti    | Park et al., 2011 |
| M. quinquenervia         | 1,8-Cineol and E-nerolidol | Aedes aegypti    | Park et al., 2011 |
| Pimenta dioica           | Eugenol, linalool | Aedes aegypti    | Perera et al., 2014 |
| P. racemosa              | Terpinem-4-ol and 1,8-cineol | Aedes aegypti    | Aciole, 2009 |
| P. guajava               | 1,8-Cineol and β-caryophyllene | Culex pipiens    | Leyva et al., 2009a |
|                         | 1,8-Cineol         | Aedes aegypti    | Lima et al., 2011 |
| P. rotundatum            | Eugenol            | Aedes aegypti    | Aguilera et al., 2003 |
| Syzygium aromaticum      | Eugenol            | Aedes aegypti    | Costa et al., 2005 |
| Orchidaceae              |                    |                  |            |
| Vanilla fragrans         | 4-ethoxyxylthiophen, 4-butoxyxylthiophen, vanillin, 4-hydroxy-2-methoxynmaldehyde and 3,4-dihydroxyphenylacetic acid | Culex pipiens | Sun et al., 2001 |
| Pinaceae                 |                    |                  |            |
| Cupressus L.             | limonene, α & β-pinene, | Aedes aegypti    | Burfield, 2000 |
| Juniperus L.             | 3-carene           | Aedes aegypti    | Burfield, 2000 |
| Pinus brutia             | α-Pinene and β-pinene | Aedes albopictus | Koutsaviti et al., 2015 |
| P. halepensis            | β-Caryophyllene    | Aedes albopictus | Koutsaviti et al., 2015 |
| P. kesiya                | α-Pinene, β-pinene, myrcene and germacrene D. | Aedes aegypti, Culex quinquefasciatus, Anopheles stephensi | Govindarajan et al., 2016 |
| P. longifolia            | L-terpinol        | Culex quinquefasciatus, Anopheles culicifacies | Ansari et al., 2005 |
| P. stankenwiczi          | Germacrene D α-Pinene and β-pinene | Aedes albopictus | Koutsaviti et al., 2015 |
| P. sylvestris            | Eugenol 3, Cyclohexene-1-methanol, α-4-trimethyl | Aedes aegypti, Culex quinquefasciatus | Fayemivo et al., 2014 |
### TABLE 1 | Continued

| Family and plant species | Major constituents | Mosquito species | References |
|--------------------------|-------------------|-----------------|------------|
| **Piperaceae**           |                   |                 |            |
| *P. auritum*             | Safrole           | Aedes aegypti   | Leyva et al., 2009b |
| *P. betle*               | Citronellal       | Aedes aegypti   | Wahyuni, 2012 |
| *P. capense*             | 2,3-Dihydro-2-(4′-hydroxyphenyl)-3-methyl-5(E)-propenylbenzofuran (conocarpan), 2-(4′-hydroxy-3′-methylphenyl)-3-methyl-5(E)-propenylbenzofuran (eupomatenoid-5), 2-(4′-hydroxyphenyl)-3-methyl-5(E)-propenylbenzofuran (eupomatenoid-6), 2,3-dihydro-5-formyl-2-(4′-hydroxyphenyl)-3-methylbenzofuran (decurrenal), and 3,7,11,15-tetramethyl-2(E)-hexadecen-1-ol (trans-phytol) | Aedes aegypti | de Morais et al., 2007 |
| *P. gaudichaudianum*     | Caryophyllene oxide, β-selinene | Aedes aegypti | de Morais et al., 2007 |
| *P. hostmanianum*        | Asaricin and myristicin | Aedes aegypti | de Morais et al., 2007 |
| *P. humayanum*           | β-selinene, caryophyllene oxide | Aedes aegypti | de Morais et al., 2007 |
| *P. klotzschianum*       | 1-Butyl-3,4-methylenedioxybenzene, | Aedes aegypti | do Nascimento et al., 2013 |
| *P. longum*              | limonene, and α-phellandrene | Culex pipiens | Lee, 2000 |
| *P. marginatum*          | Isoelemecin, apiole | Aedes aegypti | Autran et al., 2009 |
| *P. permucronatum*       | (E)-Asarone, patchouli alcohol | Aedes aegypti | de Morais et al., 2007 |
| **Plumbaginaceae**       |                   |                 |            |
| *Plumbago zeylanica*     | Plumbagin         | Aedes aegypti   | Pradeepa et al., 2016 |
| **Poaceae**              |                   |                 |            |
| *Cymbopogon citratus*    | Geranial          | Aedes aegypti   | Cavalcanti et al., 2004 |
| *Cymbopogon flexuosus*   | citral a-pinene   | Aedes aegypti   | Syed and Leal, 2008 |
| *Cymbopogon nardus*      | Geranial; neral   | Aedes aegypti   | Vera et al., 2014 |
| *Vetiveria zizanioides*  | Citronellal       | Aedes aegypti   | Carreño-Otero et al., 2018 |
| **Papilionaceae**        |                   |                 |            |
| *Neorautanenia mitis*    | Neotenone, neorautanone, pterocarpans neoduline, nepseudin,4-methoxyneoduline | Culex quinquefasciatus, Anopheles gambiae | Joseph et al., 2004 |
| **Rutaceae**             |                   |                 |            |
| *Chloroxylon swietenia*  | Heptacosanoic acid | Aedes aegypti, Culex quinquefasciatus | Balasubramani et al., 2015 |
| *Citrus aurantifolia*    | Geijerene, Limonene, Germacrene D | Aedes aegypti, Anopheles stephensi | Kiran et al., 2006 |

(Continued)
| Family and plant species | Major constituents | Mosquito species | References |
|-------------------------|--------------------|-----------------|------------|
| F. limonia              | n-hexadecanoic acid | Culex quinquefasciatus | Rahuman et al., 2000 |
| Ruta graveolens         | Undecan-2-one      | Aedes aegypti    | Tabanca et al., 2012b |
| Swinglea glutinosa      | β-Pinene; piperitenone; α-Pinene | Aedes aegypti | Vera et al., 2014 |
| Todtalia asiatica       | Linalool           | Aedes aegypti    | Nyahanga et al., 2010 |
| Zanthonyx armatum       | Linalool           | Aedes aegypti    | Tiwary et al., 2007 |
| Z. avicennae            | 1,8-Cineole, Limonene, Methyl heptyl ketone | Aedes aegypti | Prasawat et al., 2007 |
| Z. piperitum            | Asarinin, sesamin and (+)-xanthoxyl-γ,γ-dimethylallylether | Aedes aegypti, Culex quinquefasciatus | Kim and Ahn, 2017 |
| Z. monophyllum          | Germacrene D-4-ol and α-Cadinol | Aedes albopictus, Culex quinquefasciatus, Anopheles stephensi | Pavela and Govindarajan, 2017 |
| Santalaceae             | α-santalol         | Aedes aegypti, Culex pippens | Jones et al., 2007 |
| Santalum album          | Guaiol, elemol, and eudesmol | Anopheles stephensi, | Amer and Mehlhorn, 2006 |
| Schisandraceae          | Eugenol, α-Terpinyl acetate, Eucalypt, ol, (E)-anethole | Culex quinquefasciatus | Kimbaris et al., 2012 |
| Caparia biflora L.      | α-Humulene         | Aedes aegypti    | Souza et al., 2012 |
| Stemodia mantima        | β-Caryophyline and caryophyline oxide | Aedes aegypti | Arriga et al., 2007 |
| Tiliaeae                | N-Methyl-6b-(deca-1′,3′,5′-tri-enyl)-3b-methoxy-2bmethylpiperidine | Aedes aegypti | Bandara et al., 2000 |
| Verbenaceae             | β-amyrin and 12-oleanane 3β, 21β-diol, | Culex quinquefasciatus | Nikkon et al., 2010 |
| Lantana camara          | Bicyclogermacrene and E-caryophyline | Aedes aegypti | Costa et al., 2010 |
| Lippia alba             | Carvone; limonene  | Aedes aegypti    | Santiago et al., 2006 |
| L. gracilis             | Carvacrol          | Aedes aegypti    | Santiago et al., 2006 |
| L. origanoides          | Carvacrol; p-cymene | Aedes aegypti    | Vera et al., 2014 |
| L. javanica             | Allopurinol, camphor, Limonene, α-terpeneol, verbenone | Aedes aegypti | Mwangi et al., 1992 |
| L. microphylla          | 1,8-cineole, thymol, α-pinene | Aedes aegypti | Santiago et al., 2006 |
| L. nodiflora            | Camphor, p-cymene, γ-terpinene | Aedes aegypti | Santiago et al., 2006 |
| L. sidoides             | Thymol             | Aedes aegypti    | Costa et al., 2005 |
| Zingiberaceae           | β-Caryophyline and β-pinene | Aedes aegypti | Santos et al., 2012 |
| Alpinia purpurata       | 1H-3a,7-Methanoazulene and curcumene | Aedes aegypti | Choochote et al., 2005 |
| Curcuma aromatica       | Turmerone, curcumene, and zingiberene | Aedes aegypti | Leyva et al., 2008 |
| Curcuma longa           | 1,8-Cineol and p-cymene | Aedes aegypti | Prasawat et al., 2007 |
| Curcuma zedoaria        | Dodecanal          | Aedes aegypti    | Sakhanokho et al., 2013 |
| Hedychium coccineum     | 1,8-Cineol and β-pinene | Aedes aegypti | Sakhanokho et al., 2013 |
| Hedychium sp.           | 1,8-Cineol | Aedes aegypti | Sakhanokho et al., 2013 |
| Kaempferia galanga      | Ethyl trans-p-methoxyccinnamate | Aedes aegypti | Munda et al., 2018 |
| Kaempferia galanga      | Ethyl cinnamate | Aedes aegypti | Munda et al., 2018 |
| Zingiber officinalis    | 4-Gingerol         | Aedes aegypti, Culex quinquefasciatus | Rahuman et al., 2008b |
| Zingiber officinalis    | 6-Dehydrogingerdione | Aedes aegypti, Culex quinquefasciatus | Rahuman et al., 2008b |
| Zingiber officinalis    | 6-Dihydrogingerdione | Aedes aegypti, Culex quinquefasciatus | Rahuman et al., 2008b |
| Zingiber zerumbet       | α-Humulene; zerumbone | Aedes aegypti | Sutthanont et al., 2010 |
proteins, nucleic-acids, bio-membranes, besides added cellular components. Consequently, the physiology is disrupted at numerous receptor sites, eventually causing an abnormality in the nervous system. Plant metabolites affect several vital physiological functions that include inhibition of “ACHE” as well as “GABA-gated” chloride channel, disruption of Na-K ion exchange besides constricting the cellular respiration. As a subsequent event, the alteration of these enzyme levels gives rise to several anomalies that include the obstruction of nerve cell membranes and octopamine receptors along with calcium channel blockage, resulting in hormonal imbalance, mitotic poisoning, and also modifications of the molecular basis of morphogenesis (Rattan, 2010).

Synthetic insecticides generally increase the level of detoxifying enzymes. Phytochemicals target the mentioned cellular mechanisms and potentially disturb their functions (Figure 1; Zibaee and Bandani, 2010; Zibaee, 2011; Kaur et al., 2014; Senthil-Nathan, 2015). Physiological effects of phytochemicals are discussed below.

**IMPACT OF PHYTOCHEMICALS ON DETOXIFYING ENZYMES**

The antioxidant and detoxification enzymes of mosquito vectors are vital in detoxification of reactive oxygen species (ROS) synthesized by the toxic chemicals (Rattan, 2010). Esterase and phosphatase of the mosquito vectors plays a key role in several physiological events (Koodalingam et al., 2014). Excessive usage of toxic chemicals on mosquito control caused insecticide resistance through sodium channel mutations, activation of detoxification enzymes, and upregulation of key genes and other regulatory components like MicroRNAs (miRNAs). The CYP450s, GSTs, SOD, and esterase gene families are recognized as the foremost four enzymes accountable for the metabolic-resistance of the insects (Hemingway et al., 2004). Generally, detoxifying enzymes are involved in digestion, reproduction, juvenile hormone metabolism, neuronal conduction, moultong, and more importantly detoxification of toxic chemicals (Koodalingam et al., 2014). Phosphatases are involved in tissue development, cellular differentiation, carbohydrate metabolisms, and synthesis of ATP (Koodalingam et al., 2014). Mainly these two major classes of detoxifying enzymes are considered for evaluating the impact of toxic chemicals on physiological or biochemical events of arthropod vectors.

Carboxyl-esterases (EC3.1.1.1) are non-specific omnipresent enzymes that are associated to the major “endogenous” functions in insects, which hydrolyze a different carboxylic-acid ester (Lija-Escaline et al., 2015). Generally, the metabolic pathway of these enzymes was targeted by the chemical pesticides, especially the fourth generation class of Pyrethroids, which acts on the voltage sensitive sodium channels and blocks the mosquito nervous system (Hong et al., 2014). Esterases can also target by sequestering the insecticide through rapid binding and slowly releasing the insecticide metabolites (Karunaratne et al., 1993). This latter type of resistance requires the presence of increased quantities of esterase due to the 1:1 stoichiometry of the reaction and decreases the metabolic breakdown time.

Plant extracts and their derivatives have been widely reported to decrease the levels of carboxylesterase (α- β-carboxylesterase) level in the *Ae. aegypti* larva (Koodalingam et al., 2014; Lija-Escaline et al., 2015). Besides exhibiting larvicidal activity *Aalgium salvipolium*, also substantially reduced the levels of α, β-carboxylesterase as well as superoxide dismutase (SOD) in *Ae. Aegypti* (Thangaiavel et al., 2017a). *Myrrh communiphora molmol* (oil and oleo-resin extract) instigated biochemical changes in *Cx. pipiens* that affected the cell proteins, as well as loss of enzyme activity (Massoud et al., 2001).

Higher rates of enzyme activities, such as SOD (Agra-Neto et al., 2014; Lija-Escaline et al., 2015) and physiological enzymes like esterase (Wheelock et al., 2005; Lija-Escaline et al., 2015), phosphatases (Walter and Schütt, 1974; Urich, 1994) are recorded with increasing developmental stages and these are considered responsible for increased pyrethroid resistance. The Mosquito vectors that established resistance to Temephos have been found to possess genes that insensitized ACHE on exposure to pesticides. Insects were also characterized by the over expression of varied forms of detoxifying enzymes (GST, SOD, and esterases) (Larson et al., 2010).

Glutathione-S-transferases are a class of detoxification enzymes considered to play a vital role in the existence of insects exposed to toxic metabolites. Increased GST activities are connected with the expression of metabolic resistance toward insecticides (Clark, 1990). GSTs can break down a broad range of substances; amplified GST activity is possibly as a response to an environmental stress. Generally, Cytochrome P450s (CYP450) displayed upregulation when induced by plant secondary metabolites in diverse insect pests especially against the vectors of human diseases (Caballero et al., 2008) and have members which are considered as major elements conferring resistance against insecticides (i.e., CYP2, CYP4, and CYP6) (Sun et al., 2001). The upregulation of GST enzymes usually at the exposure of a prominent dosage of plant compounds suggests the activity of a major detoxification process (Edwin et al., 2016). Consequently, the levels of GST expression may be used as a biomarker to detect the development of resistance (Iukic et al., 2007).

CYP450 group of enzyme family are also designated as key indicators of metabolic resistance besides susceptibility to insecticides (David et al., 2013). Many previous research outcomes proved alteration or inhibition in the expression of major detoxifying enzymes exposed to plant chemicals. Thangaiavel et al. (2017a) showed increase in the rate of GST activity in IV instar larvae of dengue mosquito exposed to methanolic leaf extract of *J. adhatoda* with their major derivative 3-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1h) one (26.37%). Likewise, carboxylesterase activities differed significantly in *Ae. aegypti* post treatment with the leaf extracts of *P. nigrum* with their major derivatives thymol (20.77%) (Lija-Escaline et al., 2015). Correspondingly, the activity of major enzymes (esterases, GST, and CYP450) of dengue mosquito severely affected post treated with dynamic plant compound andrographolide derived from *Andrographis*
paniculata (Acanthaceae) at the maximum dosage of 12 ppm (Edwin et al., 2016). DDT resistance in the mosquito An. gambiae is correlated elevated glutathione transferase (GST) E2 activity (AgGSTE2) (Enayati et al., 2005). The DDT resistant An. gambiae evades the insecticidal activity by the dehydrochlorination of DDT to its non-insecticidal metabolite DDE. Muleya et al. (2008) reported that compounds -epiphyllocoumarin (Tral-1), knipholine anthrone, isofuranonaphthoquinones (Mr 13/2,
Mr13/4), and the polyprenylated benzophenone (GG1) were potent inhibitors of AgGSTE2.

Besides the botanical extracts, EO derived from the plants also have strong inhibition of detoxifying enzymes of arthropod vectors (Pavela, 2015). EO may provide substitute sources of vector control since they are enriched with diverse phyto-molecules with insecticidal properties (Cheng et al., 2013). Insecticide phytochemicals from EOs belong to terpenoids chiefly and Phenylpropanoids to a limited extent. In which, Terpenoids includes monoterpenes and sesquiterpenes as the major compositions of EOs (Chellappandian et al., 2018). Lee et al. (2003) specified that volatile and lipophilic monoterpenoids infiltrate insect body, where they afflict physiological processes, and hence their mode of action is hard to elucidate. Previous research of Vasantha-Srinivasan et al. (2017) showed that the CVO derived from Piper betle (L.) (Pb-CVO) showed upregulation in the level GST and CYP450 and down regulate the expression of Carboxylesterases activity against the field and laboratory strains of Ae. aegypti. Moreover, the above results also showed that the changes in the level of enzymes are steady in both field and laboratory strains compared to the chemical pesticides. Due to enriched chemical diversity and potential mosquitocidal activity, CVO have acquired greater interest from researchers looking for new besides natural replacements to chemical-pesticides in controlling medically challenging pests (Pavela, 2015). Correspondingly, EO constituent’s nootkatone and carvacrol from Alaskan yellow cedar tree inhibits 50% of acetylcholine esterase activity in Ae. aegypti compared to the carbaryl, a known acetylcholinesterase inhibitor (Anderson and Coats, 2012). The impact of major plant molecules against the mosquito larvicides was tabulated (Table 1). Hence, expression of these molecules on detoxifying and metabolic enzymes is considered an important biomarker to evaluate the mosquitocidal potential of bio-rational plant metabolites.

Pradeepa et al. (2014) have reported the antimalarial activities from the compound plumbagin, identified from the rhizome of Plumbago zeylanica against An. stephensi. Also, it was revealed that plumbagin constrains the vector AchE enzyme, An. stephensi in a dose dependent manner and also can be considered for controlling resistant vectors whose insecticide resistance is associated to an increased SOD activity (Pradeepa et al., 2016). The detection of SOD activity in the anal gills of An. stephensi larvae could be associated with their resistance provided against damaging oxygen products (Nivsarkar et al., 1991). The sensitivity of an insect to an insecticide can hence be increased by identifying certain compounds that can deactivate these enzymes (Larson et al., 2010).

**IMPACT OF PHYTOCHEMICALS ON MIDGUT TISSUES**

The midgut of the mosquito larvae is the chief interface of exterior environment and chip in major process like digestion, ion transport, absorption, and osmoregulation process (Bernick et al., 2008; Elumalai et al., 2016). Generally, gut region is the target of numerous insecticidal complexes and its integrity is dynamic for digestion and conferring of resistance against toxins (Stenfors Arnesen et al., 2008). With the insect midgut being the important site for synthesis of digestive enzymes, plant derived molecules primarily targets thee gut epithelium layer (EL) (Senthil-Nathan et al., 2008). This might be the significant cause for condensed metabolic rate in addition to a reduced enzyme activity (Selin-Rani et al., 2016). The peritrophic membrane (pM) gaurds the EL from the surrounding the gut lumen (GL) (Lija-Escaline et al., 2015). Phyto-chemicals are proven to exert a serious impact on the digestive epithelial cells and further decrease the growth rate of arthropods (Yu et al., 2015). Neira-Oviedo et al. (2008) stated that plant compounds flow into the gastric caeca and the malpighian tubules thereby affecting the midgut epithelium. For instance, extracts of M. azedarach have been reported to cause extensive harm on the EL and pM of filarial vector Cx. quinquefasciatus (Al-Mehmadi and Al-Khalaf, 2010). The pM may influence the growth and development of parasites vectors by creating a mechanical barrier to invasion by ookinetes (Rudin and Hecker, 1989). Plant extracts and their metabolites are crucial for the impairment of pest mid-gut epithelium (Rey et al., 1999). The compound cathechin isolated from Leucas aspera affects the mid-gut of the three mosquito larvae Ae. aegypti, An. stephensi, and Cx. quinquefasciatus (Elumalai et al., 2016). Previous photomicrographic study on the midgut tissues of the dengue mosquito (Field and laboratory strains of Ae. aegypti) treated with the CVO of P. betle displayed severe injuries to the GL and EL (Vasantha-Srinivasan et al., 2018). Correspondingly, leaf extracts of Aristolochia indica L. (Aristolochiaceae) and their derivatives aristolochic acid I and II showed severe damage on the midgut vacuolated gut epithelial columnar cells (epi), GL, and pM (Pradeepa et al., 2015). Likewise, methanolic leaf extracts of P. nigrum severely affected the midgut cellular organelles of Ae. aegypti at the minimal dosage of 10 ppm (Lija-Escaline et al., 2015). Similarly, Vasantha-Srinivasan et al. (2018) reported that P. betle CVO derived from P. betle at the sub-lethal dosage damage the pM, and major alteration in the alignment of EL and GL of dengue mosquito comparable to the control. Previous research on Andrographolide a major derivative of A. paniculata against dengue mosquito gut cells proved that there was an unembellished collapse in the mid-gut pM, in addition to a chief variation in the EL and GL alignment (Edwin et al., 2016), Selin-Rani et al. (2016) reported that the active plant molecules may damage the gut epithelium is the vital reason for concentrated metabolic rate and decrease in the enzyme-activity. Midgut cell damage is directly linked to the digestive and detoxifying enzymes dysregulation (Senthil-Nathan et al., 2008). This was also confirmed by histological studies of the mosquitoes that displayed midgut cell damage, post treatment with various botanical compounds (Yu et al., 2015). Further, treatment with plant compounds were also associated with altered protein (Fallatah, 2014) and biochemical profiles in mosquitoes (Senthilkumar et al., 2013).

Biochemical studies on Cx. pipipens exposed to Allium sativum, Citrus limon, and Bti were observed by Saeed et al. (2010). Results revealed that the use of plant oil extracts and Bti have great effect on total protein content of treated mosquito
larae. Fallatah (2010) reported the effect of water extract of fenugreek have high larvicidal effect against Cx. quinquefasciatus, causing noticeable effects on numerous body tissues together with the midgut and nervous system as well as total protein content. Aristolochic acids isolated from A. indica Linn, mainly affected the midgut EL and secondly the larval muscles and cells (Pradeepa et al., 2015). Similar results were also observed in mosquitoes treated with plant extracts (Costa et al., 2012). The orientation of the cytoplasmic protrusions of the apical surfaces of columnar cells toward the lumen suggests the secretion of apocrine and/or apoptosis.

Al-Mekhlafi (2018) reported the effect of Arum copticum (Apiaceae) extract against Culex pipiens larvae. Apart from exhibiting larvical activity, the extract was able to display cytopathological alterations of the midgut epithelium. EO and enriched fraction of Peumus boldus displayed larvicidal activity against Cu. Quinquefasciatus. The treated larvae displayed morphological changes in the midgut cells (de Castro et al., 2016). Velu et al. (2015) tested the peel extract of A. hypogaea against Ae. aegypti and Anopheles stephensi. The histopathological studies exposed midgut tissue damage and cuticle injury. Costa et al. (2012) reported similar aberrations in Ae. aegypti larvae (III instar) treated with Anmona coriacea extract. Ae. aegypti larvae exposed to squamocin from Annona mucosa Jacq. (Annonaceae) displayed larvicidal and cytotoxic action with changes in the midgut epithelium and digestive cells by increasing the expression of autophagy genes (Costa et al., 2014, 2017). da Silva Costa et al. (2018) also reported that squamocin affected the osmoregulation and ion-regulation of Ae. aegypti larvae which resulted in a lethal effect caused by the development of a great vacuolization in the anal papillae wall.

The histopathological study of Ae. aegypti treated with methanol extract derived from seaweeds Sargassum binderi showed that larvae treated with seaweed extracts had cytopathological alteration of the midgut epithelium. The morphological observation revealed that the anal papillae and terminal spiracles of larvae were the common sites of aberrations (Yu et al., 2015). Phytochemicals (oleic, linoleic, linolenic, palmitic, and stearic acids) and their respective methyl esters were tested against fourth instar Cu. quinquefasciatus larvae. The compounds were found to affect its metabolism and the morphology of midgut along with their fat body (de Melo et al., 2018).

**IMPACT OF PHYTOCHEMICALS ON THE INSECT BEHAVIOR**

With the development of resistance by this time attained to almost all available chemicals, strategies integrating “plant derived” compounds to influence “semiochemical”-mediated behaviors by means of interruption of mosquito-olfactory sensory system have substantially developed (Muema et al., 2017). As a consequence, the physiological status related to the olfactory sensory system is disrupted. The phytochemicals will bind to these odorant chemoreceptors and subsequent flight orientations of the mosquitoes are hindered (Bohbot et al., 2010). Henceforth the physiological status for instance “circadian-regulated appetitive stimulus” or “gonotrophic status” that triggers olfaction in pursuit of nutritious sources, mates and oviposition sites are disturbed. Plant-based semiochemicals can be exploited to lure the mosquitoes to an insecticide trap, thereby forming an integral part of an integrated vector control programme (Kamala-Jayanthi et al., 2015). Rice volatiles on evaluation with BioGent (BG) sentinel traps elicited antennal responses that stimulated long range oviposition site seeking behavior. Also, p-cresol, from Bermuda grass hay infusion was reported with avoidance response to gravid An. Gambiae (Eneh et al., 2016).

**FUTURE PERSPECTIVES**

Higher rates of anthropogenic activities that are expected to expand with the population increase will increase the incidence of vector borne diseases. Additionally, the development of resistance among the vector population against the synthetic chemical insecticides along with their persistence in the environment and toxicity for non-target organisms are reducing the efficiencies of vector management practices globally. Hence novel plant-based compounds that are safe and effective are being focused for the development of improved management of vectors.

The research has now moved on from the isolation of bioactive compounds with anti-vector potentials to formulate novel application methods. Apart from the direct application of plant metabolites in vector control, nanoparticles (NPs) synthesized from plants using green technology are emerging as a new trend. Nanotechnology is presently “revolutionizing” the manufacture of commercial pesticides. Production of green NPs and nanoencapsulation compounds upsurges the permanence of EOs through “slow-release” phenomenon deliberating sustained fortification against mosquito bites. As reported by Jinu et al. (2018), silver nanoparticles (AgNPs) from Cleistanthus collinus Karra and Stychnos nux-vomica Linn nux-vomica presented highest larvicidal activity against A. stephensi and A. aegypti. Murugan et al. (2018a,b) proved the efficacy of zinc oxide NPs fabricated using the brown macroalga Sargassum wightii Greville ex J. Agardh. against An. stephensi. In another study reported by Murugan et al. (2018b), Poly (Styrene Sulfonate)/Poly (allylamine hydrochloride) encapsulation of TiO₂ NPs were found to enhance their toxicity against mosquito vectors of Zika virus.

**CONCLUSION**

Mosquito vector borne diseases are a major human health problem in all countries. There has been an alteration toward plant-based insecticides to overcome the problems related with the use of synthetic mixtures in mosquito control programme. Botanicals can be used as mosquitocides for killing both larvae and adult mosquitoes. However, only very few botanicals have moved from laboratory to the field use, which may be due to the light and heat variability of phytochemicals compared to synthetic insecticides. Further these botanicals have been widely explored, but only a comparatively small number of patents have
been filed with the persistence of regulating the formulations for use against mosquito species in the field level.

Although the activity of phytochemicals are generally attributed to some specific compounds, but there is increasing evidence that the combination of botanicals and biocides will result in an increased bioactivity compared to single phytochemicals (Senthil-Nathan et al., 2005a; Senthil-Nathan and Kalaivani, 2005, 2006).

At present, botanical insecticides make <1% of the world’s pesticide market (Sola et al., 2014). Isolation of active principles and synthesis of secondary metabolites of botanicals against mosquito threat are very important for the management of vector borne diseases. The positive results of initial studies on larvicidal potential of botanicals encourage further interest to investigate the bioactive compounds. Identifying botanical insecticides that are effective as well as appropriate and adaptive to overcome ecological hazards, biodegradable, and have a broad spectrum of larvicidal properties will work as a new defense in the arsenal of insecticides and it may act as an appropriate alternative product to fight against vector-borne diseases.

Thus, the present review collects important information on plant extracts along with their active molecules as agents affecting the physiology and behavior of medically threatening mosquito vectors. Now collective efforts are needed to take advantage of the accumulated knowledge on phytochemical action on mosquitoes in order to integrate their application in integrated pest management programs.

AUTHOR CONTRIBUTIONS

SS-N collected all the information and wrote the review.

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**Conflict of Interest:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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