Natural Product Pesticides: Their Development, Delivery and Use Against Insect Vectors

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Abstract: Natural chemicals have considerable potential for vector management because these chemicals are safer than conventional insecticides on account of their rapid environmental biodegradation and low toxicity to natural enemies, humans and other mammals and they suffer less from problems of registration difficulties. However, isolation and chemical characterization of the active compounds from plants with strong biological activities can be a tedious process compared to synthesizing new synthetic compounds because natural compounds are generally isolated in small amounts. In addition, the purity of natural products is highly variable and is dependent upon the extraction method, plant part, plant age, geographic origin and location, climate and the overall growth and health of the plant from which the chemical is extracted. Furthermore, the research and development of natural pesticides against insect vectors is constrained because of the perceived lack of economic return to the manufacturers on investment in insect vector control and also due to the difficulties in registration. Despite these difficulties, research in plant-derived pesticides has increased considerablly. In this paper we provide an overview of the compounds isolated from plants that have been evaluated for control of insect vectors of human and animal pathogens.

Keywords: Natural pesticides, plant chemicals, essential oils, insect vectors.

1. INTRODUCTION

Insects are our chief competitor for food and fiber resources throughout the world. In addition insects are the principal vectors of the pathogens causing many human, animal, and plant diseases. Insect transmitted pathogens such as those causing malaria, dengue fever, Lyme disease, West Nile virus, Rift Valley fever, chikungunya, yellow fever, and leishmaniasis kill millions of people annually throughout the world. Nearly half of the world's population is infected with at least one type of insect-borne pathogen [1]. Malaria alone infects over 300 million people per year, striking disproportionately in areas of poverty and lower economic growth [2] and is regarded as one of the top three causes of communicable illness worldwide. It has been estimated that 1 million children in sub-Saharan Africa die each year from malaria [3]. Dengue virus and the resulting severe form of dengue hemorrhagic fever, has experienced an expanding geographic range in recent decades as the principal vector, *Aedes aegypti*, has returned to regions where it was once eliminated [4].

Recent studies indicate there are now over 500 insect and mite species resistant to pesticides [5-9]. Incidence of multiple resistance (resistance to more than one pesticide and to pesticides in more than one chemical class) is increasing rapidly. Management of insects through the use of natural product pesticides is a highly desirable component of pest management strategies which provide useful alternative or supplement to conventional insecticides. These chemicals are more desirable than conventional insecticides on account of their rapid environmental biodegradation and low toxicity to non-target organisms [10-15]. The traditional sources of natural pesticide discovery have been plants because plants have evolved a range of adaptations to improve their survival and reproduction by reducing the impact of herbivores. Plants defend themselves against damage caused by herbivory by producing secondary metabolites which influence the behavior, growth, or survival of herbivores. These chemical defenses can act as repellents or toxins to herbivores, or reduce plant digestibility. These secondary compounds represent a large reservoir of chemical structures with biological activity [16-19]. This paper will provide an overview of the compounds isolated from plants that have been evaluated for control of insect vectors of human and animal pathogens. The majority of plant extracts known to have insecticidal activities against vectors can be grouped into three categories that include the alkaloids, phenoilics and terpenoids.

2. ALKALOIDS

Alkaloids are nitrogenous compounds that show insecticidal properties at low concentration and are often toxic to vertebrates [20]. Nicotine (Fig. **1A**), ryanodine (Fig. **1B**), anabasine (Fig. **1C**) are common alkaloids used as pesticides. The mode of action of alkaloids on insect vectors varies by the structure of their molecules, but many are reported to affect acetylcholinestrase or sodium channels [21, 22].

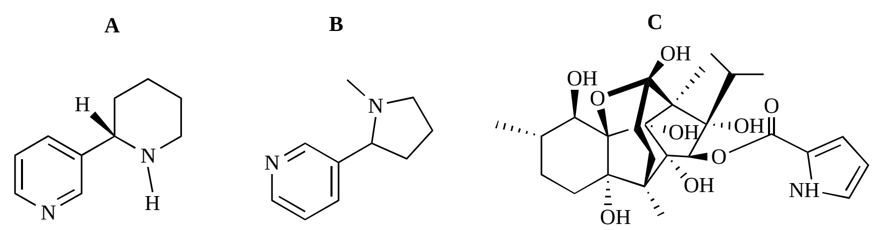

Fig. (1). Structures of nicotine (**A**), ryanodine (**B**), anabasine (**C**).

3. PHENOLS

Phenols are a class of chemical compounds consisting of hydroxyl group (-OH) attached to an aromatic hydrogen group. Within the phenoilcs, the flavinoids are known to possess insecti-

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cidal properties. A mitochondrial poison "Rotenone" from *Derris eliptica* is the most recognized example of a toxic flavonoid (Fig. **2**). The flavones from the families Labitae, Umbelliferae and Compositae and tannins present in all plants are other phenolic compounds known to possess insecticidal properties [20].

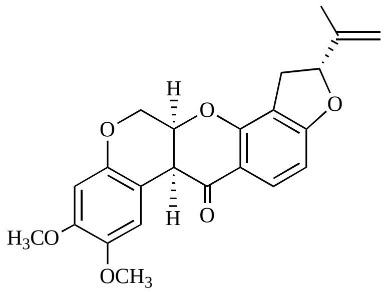


Fig. (2). Structure of rotenone.

4. TERPENOIDS

Terpenoids are among the most widespread, structurally diverse, plant produced natural pesticides. A triterpinod obtained from the neem tree, *Azadirachtin indica*, and several monterpenes such as citronella, pinene, linalool, geraniol, citronelol, limonene, myrcene and citral from essential oils and pyrethrins from various *Chrysanthemum* spp. are common terpenoids known to possess insecticidal properties. The prospective protective effects of plant chemicals against insect pests ranges from repellency expressed as feeding and oviposition deterrence, to interference with growth and development or ultimately, acute toxicity. One of the earliest reports on the use of plant extracts against insect vectors is of alkaloids including nicotine, anabasine, methylanabasine and lupinine, extracted from the Russian weed *Anabasis aphylla* and used against *Culex pipiens*, *Cu. territans*, and *Cu. quinquefasciatus* larvae [23]. Sukumar *et al*. reviewed the use of plant extracts against mosquitoes and listed 344 plant species with toxic, repellent, growth inhibition or oviposition deterrent activities [24].

5. DESCRIPTION OF SOME NATURAL PESTICIDE COMPOUNDS

5.1. Pyrethrum

Pyrethrum is the most widely used commercial natural pesticide in vector control. Pyrethrum also is known to affect insect behavior by causing avoidance or excite-repellency reactions (25-27]. Pyrethrum has been used as an insecticide since the early 1800's to control body lice in Persia and later to repel mosquitoes by incorporating ground pyrethrum flowers into mosquito repellent coils [28]. In fact, pyrethrum was presumed to be the most economically viable pest control agent prior to the invention of synthetic insecticides [28-30]. Although pyrethrum consumption was greatly reduced with the advent of synthetic pyrethroids, pyrethrum continues to be the most predominant botanical product used in pest management, accounting for 80% of the global botanical insecticides (12). Pyrethrum refers to the oleoresin extracted from the dried flowers of the pyrethrum daisy, *Tanacetum cinerariaefolium* (Asteraceae). Chemically, pyrethrum contains six closely related insecticidal esters, collectively referred to as the pyrethrins, which differ only in the terminal substituents in the side chains of the acid and alcohol components (Fig. **3**, **A**-**F**). The six individual pyrethrins are pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II [28-31]. Among the six esters, pyrethrins I and II, are the most abundant and account for most of the insecticidal activity [29-31]. The insecticidal action of the pyrethrins is characterized by a rapid knockdown effect, particularly in flying insects, and hyperactivity and convulsions in most insects. Pyrethrum affects the central nervous system of insects by blocking the sodium gated nerve junctions to impair the nerve impulses [32]. Pyrethrum rapidly knocks down and kills a wide variety of insect pests, such as cockroaches, mosquitoes, fleas, and house flies [33].

Pyrethrins are very important insecticides because of their rapid paralysis of flying insects, relatively low mammalian toxicity, and rapid rate of degradation in the environment [28, 30, 31, 34, 35]. They are typically used as insecticides for both home and commercial use [31]. However, a major use of pyrethrum is in public health, treatment of animal premises and structural pest control [12, 31, 32]. Pyrethrins are often synergized with piperonyl butoxide to enhance the effectiveness of pyrethrins. Piperonyl butoxide works to block different biochemical pathways in insects and restricting the insect's ability to detoxify the pyrethrins by inhibiting the mixed function oxidase enzymes [29-31].

Pyrethrum plants have historically been grown in commercial quantities in Kenya, Tanzania, Rwanda, Papua New Guinea, Tasmania Uganda and Australia [28, 36]. Pyrethrum in kerosene emulsions were extensively used in the US in the 1930's in large-scale larviciding operations, but since this time, such applications have been utilized predominantly against adult mosquitoes [37]. Pyrethrum first was used successfully in vector control operations in South Africa and later in India [38-42]. Pyrethrum extract is still used in antimalarial programs in India [42]. High target insect mortality at an extremely low concentration of active ingredients partially offsets the greater cost of pyrethrum, allowing this product to compete with synthetic adulticiding materials (37). Duchon *et al*. [27] suggested use of pyrethrum for the impregnation of bed nets and for personal protection due to its high toxicity and excito-repellency against insecticide-resistant mosquitoes. Despite its long history of use, few cases of specific resistance against insect vectors to pyrethrum have been reported [27, 43].

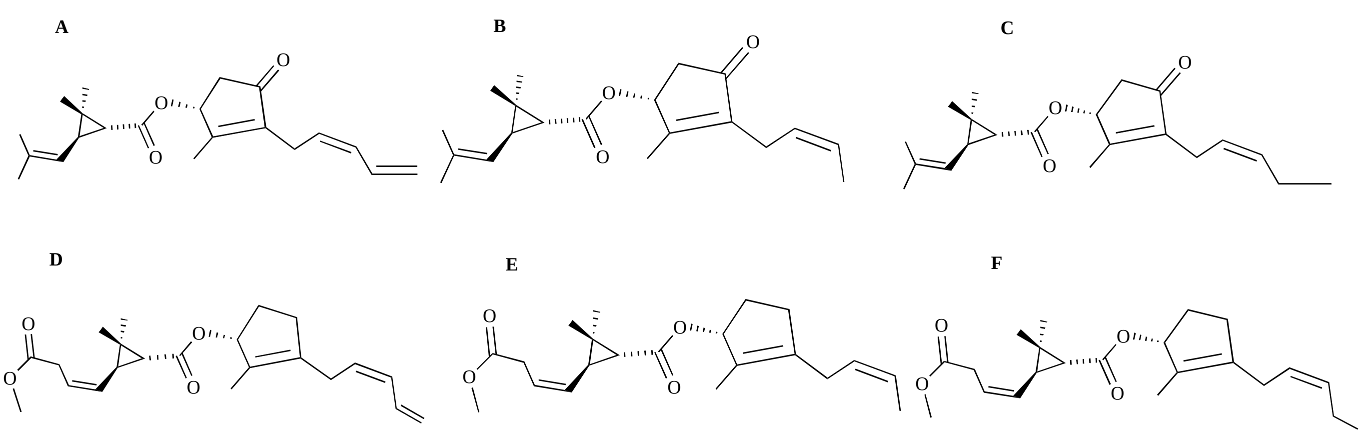
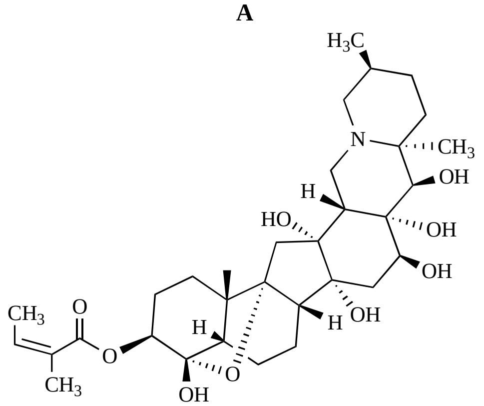


Fig. (3). Structures of pyrethrins: pyrethrin I (**A**), cinerin I (**B**), jasmolin I (**C**), pyrethrin II (**D**), cinerin II (**E**), jasmolin II (**F**).



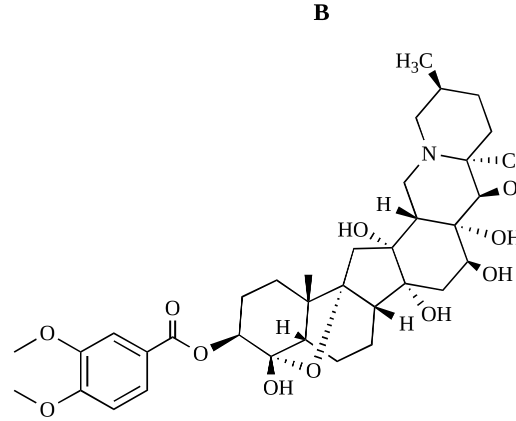


Fig. (4). Structures of cevadine (**A**), veratridine (**B**).

5.2. Nicotine, Rotenone, Rynadine And Sabadilla

Nicotine (Fig. **1A**), rotenone (Fig. **2**), and ryanodine (Fig. **1B**) are other older botanical that have been used in vector control since ancient times. Nicotine and the related alkaloids nornicotine and anabasine are highly insecticidal constituents obtained from aqueous extracts of tobacco (*Nicotiana* spp.; Solanaceae) and *Anabasis aphylla* (Chenopodiaceae) [44]. These three alkaloids, are synaptic poisons that mimic the neurotransmitter acetylcholine. Rotenone is an isoflavonoid obtained from the roots or rhizomes of tropical legumes in the genera *Derris*, *Lonchocarpus* and *Tephrosia*. Rotenone is a broad-spectrum electron transport chain inhibitor insecticide. Nicotine is extremely toxic to mammals (rat oral LD_{50} is 50 mg kg^{-1}) and is rapidly absorbed through the eyes, skin, and mucous membranes [23, 45] whereas rotenone is highly toxic to both mammals and fishes [46, 47].

Ryanodine is an alkaloid obtained from *Ryania speciosa* and is reported to kill mosquito larvae by acting on Ca^{++} channels [48]. The extract contains several structurally related ryanoids, including: ryanodine, 10-(O-methyl)-ryanodine, 9, 21-dehydroryanodine, and ryanodol. The most toxic and abundant compounds in the extract are ryanodine and 9, 21-dehydroryanodine, and thus they account for virtually all of the insecticidal activity. The compound has extremely high affinity to the ryanodine receptor, a group of calcium channels found in skeletal and heart muscle cells [51].

Sabadilla is one of the least toxic registered botanical insecticides to mammals [52]. Sabadilla is obtained from the seeds of plants belonging to the genus *Schoenocaulon*. The activity of sabadilla is primarily due to the alkaloids cevadine (Fig. **4A**) and veratridine (Fig. **4B**) which typically exist in a 2:1 ratio and are collectively referred to as veratrine. The two most important compounds are the lipophilic alkaloids veratridine and cevadine, with veratridine having greater insecticidal potency [53]. The mode of action of sabadilla alkaloids is believed to be similar to that of the pyrethrins [31]. Sabadilla breaks down rapidly in sunlight. The major effects of sabadilla poisoning include muscle rigor in mammals and paralysis in insects. Sabadilla extract is much less toxic to mammals than most other insecticides; however, it may have a sneeze-inducing effect in mammals when inhaled, as a result of irritating the mucous membranes. Additionally, it is very toxic to honeybees [51].

5.3. Neem

Azadirachta indica (Neem) is a tree in the mahogany family *Meliaceae* [54, 55]. Native to the Indian subcontinent, this fast-growing shade tree has been widely cultivated in Africa, Australia, the Caribbean, and Central and South America. Seeds and leaves of this tree have been used for centuries to control pests [56, 57]. The neem tree contains at least 35 biologically active constituents. Although the variety of active ingredients obtained from the neem tree, such as the azadirachtin, are known, it has not been possible to synthesize these complex compounds [12].

Azadirachtin is the predominant triterpenoid insecticidal active ingredient found in the seeds, leaves, and other parts of the neem tree [58]. The active site on azadirachtin is a ring C-seco tetranortriterpenoid (Fig. **5**), which has been demonstrated to strongly interfere with molting and reproduction in several insect species [57-61]. Azadirachtin and other compounds in neem products exhibit various modes of action against insects such as antifeedancy, growth regulation, fecundity suppression and sterilization, repellency or changes in biological fitness, and blocking development of vector-borne pathogens [61]. Azadirachtin has been shown to be effective against over 200 insect species in seven orders [62]. In insect vectors, neem products have been investigated for effects against mosquitoes, flies, triatomines, fleas, and lice [61-66]. A review by Mulla and Su listed the efficacy of neem products against the aforementioned groups, as well as sand flies, house flies, cockroaches, and ticks and hence will not be a focus of current paper [61]. Neem has several properties desireable in a natural insecticide however, as with pyrethrum, neem has several drawbacks including limited persistence under ultraviolet light, temperature, pH and microbial degradation. Furthermore, manufacturing of neem products is still dependent on natural sources because the chemical structure of azadirachtin is too complicated for synthesis [61,62].

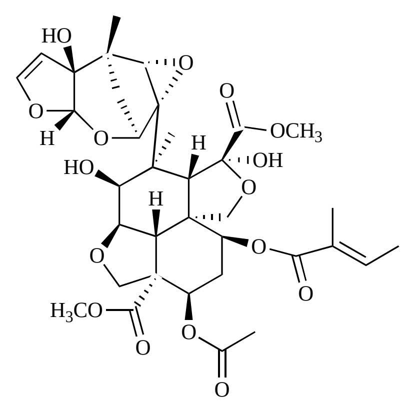


Fig. (5). Structure of azadirachtin.

5.4. Essential Oils and their Constituents

Essential oils and their derivatives are considered to be an alternative means of controlling many harmful insects [13, 67]. Essential oils are volatile, natural, complex compounds characterized by a strong odor and are formed by aromatic plants as secondary metabolites [13, 68]. They are lipophilic in nature and interfere with basic metabolic, biochemical and physiological and behavioral functions of insects [69]. In nature, essential oils protect plants from herbivores and microorganisms through their antimicrobial or insecticidal properties. Nearly 3,000 essential oils are known from nearly 17,500 aromatic plant species out of which about 300 are commercially important for pharmaceuticals, pesticide or flavor industries [13, 68, 70, 71]. Thus, they are generally recognized as safe by the US Food and Drug Administration [72].

The majority of essential oils originate in the plant families: Myrtaceae, Lauraceae, Rutaceae, Lamiaceae, Asteraceae, Apiaceae, Cupressaceae, Poaceae, Zingiberaceae and Piperaceae [13, 73]. Essential oils exist in wide variety of structures with diverse functions and are often classified into four main groups: terpenes, benzene derivatives, hydrocarbons and other miscellaneous compounds [13, 74]. Their composition may vary considerably between aromatic plant species and varieties, and within the same variety from different geographic areas [75]. Composition, quality, and quantity of essential oils is known to depend on several factors including extraction methods, source, plant growth, climate, plant structure and the vegetative stage of source plant [13, 76, 77].

Essential oils are presumed to interfere with basic metabolic, biochemical, physiological and behavioral functions of insects [13, 69]. However, little is known about the true mode of action of essential oils on insects. The rapid onset of toxic signs suggests a neurotoxic mode of action involving competitive inhibition of acetylcholinesterase [78-80] competitive activation of octopaminergic receptors [80-82] or interference with GABA-gated chloride channels [83]. Linalool a constituent of several essential oils has been demonstrated to act on the nervous system, affecting ion transport and the release of acetylcholine esterase [79] whereas eugenol has been shown to mimic octopamine in *Periplaneta americana* and *Drosophila melanogaster.* Toxicity of eugenol increased in octopamine deficient mutant *D. melanogaster* [79-82]. Thymol modulated GABA receptors in *D. melanogaster* [83]. Rey et al and David *et al.* found that tannic acid from decaying leaves of *Alnus glutinosa, Populus nigra,* and *Quercus robur* primarily affect the midget epithelium and secondarily affect gastric caeca and the malpighian tubules in mosquito larvae [83-85]. Toxic, repellent, ovicidal or growth retardant activity of large number of essential oils or their constituents have been demonstrated on large number of haematophagous insects including mosquitoes, fleas, lice, filth flies, ticks and mites [86-94]. However, in insect vectors the bioactivity of essential oils has been evaluated primarily against mosquitoes and to a lesser extent on other insect vectors, perhaps because of their greater significance in pathogen transmission.

5.4.1. Toxic Activity

5.4.1.1. Toxicity Activity on Mosquitoes

Toxic activity of essential oils on mosquitoes has been reviewed by Sukumar *et al.* and Shallan *et al.* [24, 95]. A survey of the literature on insecticidal properties of essential oils from the year 2004 onwards indicates that essential oils from about 90 plant genera belonging to 38 plant families were reported to have toxic properties against mosquito larvae (Table **1**). Although the majority of essential oils are less toxic than synthetic insecticides, LC_{50} values as low as 0.004 mg L^{-1} from pipercide from *Piper nigrum* against *Cx. pipiens pallens* larvae have been reported [155]. Komalamisra *et al.* evaluated 84 Thai plant species against *Ae. aegypti, Cx. quinquefasciatus, An. dirus and Mansonia uniformis* larvae, of which *Rhinacanthus nasutus* extract exhibited strongest larvicidal activity with LC_{50} values ranging between 3.9 and 11.5 mg L^{-1} [156]. Pulegone, thymol, and eugenol extracted from rosemary oil showed high larvicidal activity against multiple larval stages of *Ae. aegypti* [157]. The LC50 values for these compounds ranged from 10.3-40.8 mg L^{-1} and 2.3-3.2 mg L^{-1} against third and first instar larvae, respectively. Piperitenone oxide isolated from *Mentha spicata viridis* showed high larvicidal and adulticidal activities against *An. stephensi* [158]. Essential oils from *Citrus hystrix, C. reticulata, Zingiber zerumbet, Kaempferia galanga,* and *Syzygium aromaticum* showed toxicity to permethrin resistant *Ae. aegypti* [159]. Pellitorine, a chemical isolated from *Asarum heterotropoides* roots showed comparable toxicity to laboratory susceptible and fenthion, chlorpyrifos, fenitrothion, deltamethrin, chlorfenapyr, and α-cypermethrin resistant *Cx. pipiens* pallens, *Ae. aegypti*, and *Oc. togoi* mosquitoes [160].

A majority of studies have concentrated on the evaluation of essential oils as larvicides; however, essential oils from *Aristolochia indica, Cassia angustifolia, Diospyros melanoxylon, Dolichos biflorus, Gymnema sylvestre, Justicia procumbens, Mimosa pudica, Zingiber zerumbet* also exhibited good activity against *Cx. gelidus* and *Cx. quinquefasciatus* adults [106]. The essential oil of *Curcuma zedoaria* generated an LC_{50} ranging from 5.44-8.52 g mg^{-1} of body weight against *Ae. aegypti* adults. These toxicity doses are comparable to many synthetic insecticides including permethrin and imidacloprid [161]. Kaufman *et al.* reported that geranyl aetone, citronellol, beta damascene and rosalva were highly toxic to *Ae. aegypti, An quadrimaculatus* and *Ae. albopictus* adults in laboratory as well as in field evaluations with stability up to 8 days under laboratory conditions [94]. Terpenoid compounds from clove, coriander, thyme, parsley and anis oils provided high larvicidal activity against *Ochleotatus caspius* with LC_{50} values ranging from of 7.5 mg L^{-1} to 156 mg L^{-1} [122]. Anthraquinone compound, Emoien isolated from *Cassia nigricans* exhibited LC_{50} values as low as 2.4 mg L^{-1} against Anopheles gambiaea larvae [162]. Similarly, piperolein-A and piperine extracted from *Piper nigrum* exhibited LC_{50} values as low as 1.46 and 1.53 mg L^{-1}, respectively, against *Ae. aegypti* [163].

5.4.1.2. Toxic Activity on other Haematphagous Arthropods

Essential oil from *Eucalyptus globulus* showed higher toxicity (0.125 mg cm^{-2}) against *Pediculus humanus capitis* than the commercially used pediculides delta-phenothrin or pyrethrum (0.25 mg cm^{-2}) [164]. Essential oils from *Cinnamomum camphora, Allium cepa, Matricaria piperita, M. chamomilla* killed 100% of adult buffalo lice, *Haematopinus tuberculatus* within two minutes under laboratory conditions. Choi *et al.* reported that essential oils from *Eugenia caryophyllata,* and *E. globulus* provided high mortality to d-phenothrin and pyrethrum resistant (resistance ratios up to 754) *P. humanus capitis* [165]. Mann *et al.* [93] reported that geranyl aetone, citronella and rosalva were highly toxic to *Musca domestica* and *Stomoxys calcitrans.* The LC_{50} values for these chemicals ranged between 16.30 to 40.41 and 25.98 to 50.02 μg cm^{-2} against *M. domestica* and *C. stomoxys,* respectively. Furthermore these compounds were only 35 times less toxic than permethrin on field collected permethrin resistant strains of *M. domestica*. Palacio *et al.* reported that essential oils from *C. aurantium* (LC_{50} value 4.8 mg dm^{-3}) and *C. sinensis* (LC_{50} value 3.9 mg dm^{-3}) were highly toxic to *M. domestica* [117].

Although essential oils or their constituents possess good efficacy and are environmentally friendly, the majority of the essential oils are less effective than synthetic insecticides. Thus essential oil products might be better used in combination with synthetic insecticides rather than stand-alone products. Furthermore, essential oils may be used in rotation with synthetic insecticides for vector control strategies, especially in light of documented insecticide resistance of several active ingredients against haematophagous insects [95].

5.4.2. Repellent Activity

5.4.2.1. Repellent Activity on Mosquitoes

Essential oils of large number of plants have been found to have repellent properties against various haematophagous arthropods (Reviewed by Nerio *et al.* and Adorjan and Buchbauer) [166, 167]. The oils, which have been reported as potential sources of

Table 1. Insecticidal Activity of Plant Essential Oils Against Adult Mosquitoes

Plant Species	Plant Family	Insect Species	LC_{50} mg L^{-1}	Reference
Aegle marmelos	Rutaceae	*An. subpictus*	167.0	96
		Cx. tritaeniorhynchus	99.0	
Ageratum conyzoides	Asteraceae	*Ae. aegypti*	148	97
Alpinia speciosa	Zingiberaceae	*Ae. aegypti*	32.0	98
Amyris balsamifera	Rutaceae	*Cx. quinquefasciatus*	170.7	99
Am. balsamifera	Rutaceae	*Ae. aegypti*	52.0	100
		Ae. albopictus	78.0	
		Cx. pipiens allans	77.0	
Apium graveolens	Umbelliferae	*Ae. aegypti*	42.1	101
		An. dirus	59.4	
Anacardium occidentalis	Anacardiaceae	*Ae. aegypti*	14.5	102
Andrographis paniculata	Acanthaceae	*An. subpictus*	67.2	96
		Cx. tritaeniorhynchus	88.5	
Angelica purpuraefolia	Apiaceae	*Ae. aegypti*	31.2	103
Annona glabra	Annonaceae	*Ae. aegypti*	27.0	104
Anthemis nobilis	Asteraceae	*Cx. quinquefasciatus*	108.7	105
Aquilaria malaccensis	Thymelaeaceae	*Ae. aegypti*	20.2	102
Artemisia nilagirica	Asteraceae	*Ae. albopictus*	5.0	105
Aristolochia indica	Aristolochiaceae	*Cx. gelidus*	12.5	106
		Cx. quinquefasciatus	25.6	
Asarum heterotropoides	Aristolochiaceae	*Cx. pipiens*	2.2	107
		Ae. aegypti,	23.8	
		Oc. togoi	3.1	
Asarum heterotropoides	Aristolochiaceae	*Cx. pipiens*	25.1	108
Auxemma glazioviana	Boraginaceae	*Ae. aegypti*	2.53	109
Canna indica	Cannaceae	*An. stephensi*	29.6	106
		Cx. quinquefasciatus.	40.8	
Cannabis sativa	Cannabaceae	*Cx. quinquefasciatus*	127.3	99
Carapa guianensis,	Meliaceae	*Ae. aegypti*	57.0	104
Carum carvi	Umbelliferae	*Ae. aegypti*	54.6	101
		An. dirus	72.9	
Cassia angustifolia	Caesalpinaceae	*Cx. gelidus*	17.9	106
		Cx. quinquefasciatus	34.8	
Cedrus libani	Pinaceae	*Cx. pipiens*	47. 8	110
Chenopodium ambrosioides	Chenopodiacea	*An. arabiensis*	17.5	111
		Ae. aegypti	9.1	
Chenopodium ambrosioides	Chenopodiacea	*An. gambiae*	18.3	112
Chloroxylon swietenia	Rutaceae	*An. gambiae*	1.0 (μg cm^{-3})	113
		Cx. quinquefasciatus	1.2	
		Ae. aegypti	1.7	
Cinnamomum osmophloeum	Lauraceae	*Ae. aegypti*	36.0	114
C. cassia	Lauraceae	*Ae. aegypti*	80.0	101
		Ae. albopictus	84.0	
		Cx. pipiens	66.0	
C. iners	Lauraceae	*Ae. aegypti*	62.8	102
C. kuntsleri	Lauraceae	*Ae. aegypti*	105.9	102

Table 1. contd….

Plant Species	Plant Family	Insect Species	LC_{50} mg L^{-1}	Reference
C. pubescens	Lauraceae	*Ae. aegypti*	25.6	102
C. scortechinii	Lauraceae	*Ae. aegypti*	70.1	102
C. sintoc	Lauraceae	*Ae. aegypti*	35.6	102
C. zeylanicum	Lauraceae	*Ae. aegypti*	86.8	102
C. osmophloeum	Lauraceae	*Ae. albopictus* *Cx. quinquefasciatus Armigeres subal-batus*	40.8 31.3 22.1	115
C. osmophloeum	Lauraceae	*Ae. aegypti*	36.0	114
Citrus aurantium	Rutaceae	*Cx. quinquefasciatus*	179.8	99
C. aurantium	Rutaceae	*Cx. pipiens pallens*	39.8	116
C. limon	Rutaceae	*Cx. pipiens pallens*	30.1	117
C. sinensis	Rutaceae	*Cx. pipiens pallens*	51.5	117
C. aurantium bergamia	Rutaceae	*Cx. pipiens*	58.0	118
C. sinensis	Rutaceae	*Cx. pipiens molestus*	60.0	119
Clausena dentata	Rutaceae	*Ae. aegypti*	140.2	120
Clitoria ternatea	Fabaceae	*An. stephensi,* *Ae. aegypti* *Cx. quinquefasciatus*	65.2 154.5 54.4	121
Cocculus hirsutus	Menispermaceae	*An. subpictus* *Cx. tritaeniorhynchus*	142.8 105.2	96
Copaifera langsdorfii	Fabaceae	*Ae. aegypti*	41.0	104
Coriander sativum	Apiaceae	*Ochlerotatus caspius*	156.0	122
C. argyrophyloides	Apiaceae	*Ae. aegypti*	102.0	123
Croton nepetaefolius	Euphorbiaceae	*Ae. aegypti*	84.0	123
C. sonderianus	Euphorbiaceae	*Ae. aegypti*	104.0	123
C. zenhtneri	Euphorbiaceae	*Ae. aegypti*	28.0	123
Cryptomeria japonica	Cupressaceae	*Ae. aegypti* *Ae. albopictus*	28.4 51.2	115
C. japonica	Cupressaceae	*Ae. aegypti*	37.6	124
Curcuma longa	Zingiberaceae	*An. gambiae*	17.0	125
C. zedoaria	Zingiberaceae	*Ae. aegypti* *An. dirus*	31.9 29.7	101
Cymbopogon citratus	Poaceae	*Cx. quinquefasciatus*	184.2	126
C. citratus	Poaceae	*Ae. aegypti*	69.0	127
C. citratus,	Poaceae	*Cx. quinquefasciatus*	165.7	128
C. nardus	Poaceae	*Ae. aegypti*	33.0	101
C. winterianus	Poaceae	*Ae. aegypti*	98.0	103
Dendropanax morbifera	Araliaceae	*Ae. aegypti*	62.3	129
Derris spp.	Leguminosae	*Ae. aegypti*	60.7	101
Dolichos biflorus	Dolichos biflorus	*Cx. gelidus* *Cx. quinquefasciatus*	33.1 37.5	106
Eclipta prostrata	Asteraceae	*An. subpictus* *Cx. tritaeniorhynchus*	78.3 119.9	86
Elaeoselinum asclepium	Apiaceae	*Cx. pipiens*	97.0	130

Table 1. contd….

Plant Species	Plant Family	Insect Species	LC50 mg L-1	Reference
Erigeron canadensis	Asteraceae	*Cx. quinquefasciatus*	141.9	99
Eucalyptus camaldulensis	Myrtaceae	*Ae. aegypti*	26.8	131
Eu. citriodora	Myrtaceae	*Ae. aegypti* *Ae. albopictus* *Cx. pipiens allans*	58.0 127.0 113.0	100
Eu. dunnii	Myrtaceae	*Ae. aegypti*	25.2	131
Eu. gunnii	Myrtaceae	*Ae. aegypti*	21.1	131
Eu. saligna	Myrtaceae	*Ae. aegypti*	22.2	131
Eu. tereticornis	Myrtaceae	*Ae. aegypti*	22.1	131
Eu. tereticornis	Myrtaceae	*An. stephensi*	50.0	132
Filipendula glaberrima	Rosaceae	*Ae. aegypti*	28.4	133
Ferula hermonis	Umbelliferae	*Cx. pipiens*	44.0	114
Foeniculum vulgare	Apiaceae	*Ae. aegypti* *An. dirus*	49.3 35.3	115
Foeniculum vulgare	Apiaceae	*Cx. pipiens*	24.5	114
Ginkgo biloba	Ginkgoaceae	*Cx. pipiens*	12.7	134
G. exocarps	Ginkgoaceae	*Cx.pipiens*	18.6	135
Homalomena propinqua	Araceae	*Ae. aegypti*	42.3	100
Ipomoea cairica	Convolvulaceae	*Cx. tritaeniorhynchus Ae. aegypti* *An. stephensi* *Cx. quinquefasciatus*	14.8 22.3 14.9 58.9	136
Juniperus communis	Cupressaceae	*Cx. quinquefasciatus*	164.3	99
Justicia procumbens	Acanthaceae	*Cx. gelidus* *Cx. quinquefasciatus*	12.0 20.8	105
Lavandula angustifolia	Lamiaceae	*Cx. quinquefasciatus*	121.6	99
Laurus nobilis	Lauraceae	*Cx. quinquefasciatus*	167.9	99
Laurus nobilis	Lauraceae	*Cx. pipiens molestus*	117.0	114
L. gracilis	Lauraceae	*Ae. aegypti*	98.0	137
L. sidoides,	Lauraceae	*Ae. aegypti*	63.0	123
Melaleuca alternifolia	Myrtaceae	*Cx. quinquefasciatus*	204.1	99
Melissa officinalis	Lamiaceae	*Cx. pipiens*	61.2	138
Mentha arvensis	Lamiaceae	*Cx. quinquefasciatus*	178.0	112
M. suaveolens	Lamiaceae	*Cx. pipiens*	47.9	138
M. spicata	Lamiaceae	*Cx. pipiens*	52.8	138
M. longifolia	Lamiaceae	*Cu. pipiens*	59.3	138
Mimosa pudica	Fabaceae	*Cx. gelidus* *Cx. quinquefasciatus*	53.5 57.4	105
Morinda citrifolia	Rubiaceae	*An. albimanus*	40.72	139
Murraya koenigii	Rutaceae	*An. stephensi*	16.0	140
Nepeta cataria	Lamiaceae	*Cx. quinquefasciatus*	112.4	99
Nepeta cataria	Lamiaceae	*Ae. aegypti* *Ae. albopictus*	70.0 298.0	100
Ocimum americanum	Lamiaceae	*Ae. aegypti*	67.0	124

Table 1. contd….

Plant Species	Plant Family	Insect Species	LC_{50} mg L^{-1}	Reference
O. basilicum	Lamiaceae	*Cx. quinquefasciatus*	26.98	119
O. basilicum	Lamiaceae	*Cx. quinquefasciatus*	171.6	99
O. basilicum	Lamiaceae	*An. quadrimaculatus*	190.0	141
O. lamiifolium	Lamiaceae	*An. arabiensis* *Ae. aegypti*	20.9 8.6	142
O. gratissimum	Lamiaceae	*Ae. aegypti*	60.0	124
O. sanctum	Lamiaceae	*Cx. quinquefasciatus*	1.1	143
Oenanthe pimpinelloides	Apiaceae	*Cx. pipiens*	40.3	120
Pelargonium citrosum	Geraniaceae	*Ae. aegypti*	25.0	101
P. graveolens	Geraniaceae	*Cx. quinquefasciatus*	226.5	125
P. roseum	Geraniaceae	*Cx. quinquefasciatus*	130.3	99
Petroselinum crispum	Apiaceae	*Oc. caspius*	24.3	118
Pimenta dioica	Myrtaceae	*Cx. quinquefasciatus*	77.2	99
Pimpinella anisum	Umbelliferae	*Oc. caspius*	65.1	118
Piper longum	Solanaceae	*Ae. aegypti*	0.24	144
P. marginatum	Solanaceae	*Ae. aegypti*	20.0	145
P. nigrum	Solanaceae	*Ae. aegypti*	0.35	146
Pinus pinea	Pinaceae	*Cx. pipiens*	75.0	104
Plectranthus amboinicus	Lamiaceae	*An. stephensi*	28.4	146
Pogostemon cablin	Labiatae	*Ae. albopictus*	60.0	147
Pogostemon cablin	Labiatae	*Ae. aegypti*	187.0	147
Ravensara aromatica	Lauraceae	*Cx. quinquefasciatus*	101.4	99
Rosmarinus officinalis	Lamiaceae	*Cx. quinquefasciatus*	111.1	99
Salvia fruticosa	Labiatae	*Cu. pipiens*	91.45	138
S. pomifera	Labiatae	*Cu. pipiens*	79.46	138
S. sclarea	Labiatae	*Cx. quinquefasciatus*	127.5	99
Santalum album	Santalaceae	*Cx. quinquefasciatus*	225.3	99
Satureja hortensis	Lamiaceae	*Cx. quinquefasciatus*	36.1	99
Tagetes patula	Asteraceae	*Ae. aegypti* *An. stephensi* *Cx. quinquefasciatus*	13.6 12.1 22.3	148
Tanacetum vulgare	Asteraceae	*Cx. quinquefasciatus*	186.6	99
Tephrosia cinerea	Fabaceae	*Ae. aegypti*	66.1	149
T. serpyllum	Fabaceae	*Ae. aegypti* *An. stephensi* *Cx. quinquefasciatus*	1.0 1.0 9.7	150
Thymus vulgaris	Lamiaceae	*Oc. caspius*	15.0	118
T. vulgaris	Lamiaceae	*Cx. quinquefasciatus*	30.3	115
T. vulgaris	Lamiaceae	*Cx. quinquefasciatus*	32.9	99
Vitex negundo	Verbenaceae	*Cx. quinquefasciatus*	4.2	143
Xylopia caudata	Annonaceae	*Ae. aegypti*	29.8	101
X. ferruginea	Annonaceae	*Ae. aegypti*	74.5	101
Zanthoxylum acanthopodium	Rutaceae	*Ae. aegypti*	19.9	101

Table 1. contd….

Plant Species	Plant Family	Insect Species	LC_{50} mg L^{-1}	Reference
Z. ailanthoides	Rutaceae	*Ae. Albopictus*	45.2	151
		Cx. pipiens	20.8	
Z. armatum	Rutaceae	*Ae. aegypti*	54.0	152
		An. stephensi	58.0	
		Cx. quinquefasciatus	49.0	
Z. armatum	Rutaceae	*Ae. albopictus*	259.0	153
		Ae. albopictus	25.0	
		Cx. pipiens	121.9	
		Cx. pipiens	29.5	
Z. articulatum	Rutaceae	*Ae. aegypti*	77.6	154
Z. limonella	Rutaceae	*Ae. aegypti*	24.6	101
		An. dirus	57.2	
Zingiber cassumunar	Zingiberaceae	*Cx. quinquefasciatus*	202.3	99
Z. officinalis	Zingiberaceae	*Cx. quinquefasciatus*	50.8	125
Z. officinalis	Zingiberaceae	*Cx. quinquefasciatus*	1.6	143
Z. zarumbet	Zingiberaceae	*Cx. gelidus*	69.2	105
		Cx. quinquefasciatus	19.3	

insect repellents, include citronella, cedar, verbena, pennyroyal, geranium, lavender, pine, cajeput, cinnamon, rosemary, basil, thyme, allspice, garlic and peppermint, among others. Lemongrass, *Cymbopogon* spp., has been reported to produce the most used natural repellents in the world [88, 166]. Essential oils from *C. martinii martinii* provided 100% repellency for 12 h against *Anopheles* mosquitoes in field tests [168]. *Cymbopogon winterianus* oil, mixed with 5% vanillin, gave 100% protection for 6 h against *Ae. aegypti, Cx. quinquefasciatus* and *Anopheles dirus* [169]. Essential oils obtained from *Eucalyptus* produced high repellency against the mosquitoes, *Ae. albopictus* and *Mansonia* spp., [170, 171]. Piperitenone oxide isolated from *Mentha spicata viridis* was found to be highly repellent against *An. stephensi* [158]. Essential oils from *C. excavatus* gave 100% repellency for 2 h, against *An. arabiensis* [172]. Essential oils of *Melaleuca ericifolia* effectively repelled *Ae. vigilax* and *Verrallina carmenti* mosquitoes [173]. Essential oils from clove, *Syzygium aromaticum* provided 2 h of complete repellency against *Ae aegypti*, *Cx. quinquefasciatus* and *An. dirus* [72]. Essential oils from catmint, *Nepeta cataria* at 15% active ingredient conferred complete protection for 7.5 h from *Ae. intrudens* under field conditions [174].

Recently several new essential oil-based chemistries have been commercialized as mosquito repellants. Examples of such chemistries are use of citronella oil alone or in combination with cedarwood or lavender, peppermint, clove, *Eucalyptus* and garlic in a number of commercial insect repellent products [175]. Commercial natural chemical based repellents such as Swamp Buddy Bug Chaser®, All Sport™, Neem Aura®, GONE®, Sun Swat™, Bite Blocker™, Cutter®, 3m™, Ultrathon™, Green Ban™ have been developed against several mosquito species [176, 177]. However, the field efficacy of these commercial products has been reported to be highly variable depending upon the insect species, product formulation and methods of evaluation. There have been numerous reports concerning the biological properties of many kinds of essential oils; however, most of the results were obtained from artificial (in vitro) testing methods using cloth, filter paper, animal membrane or olfactometry, with few from in vivo evaluations utilizing animal or human subjects [86,178]. Qualls and Xue reported that commercial products Geraniol®, All Sport™ and Swamp Buddy Bug Chaser™ provided 4, 1.5 and 1 hr protection against *Psorophora ferox*, *Ae. atlanticus*, and *Ae. mitchellae* bites [177]. However, their protective effects dissipated relatively rapidly [167, 178]. Commercial candles with 5% geraniol, linalool and citronella caused an 82, 65 and 35% respectively reduction in female mosquitoes trap catches and a 70, 49 and 15% reduction in sand fly trap catches up to a distance of 1.0 m [179]. The candles also produced comparable repellency when evaluated under high mosquito and sand fly populations [180]. However, a continuous release diffuser containing these essential oils provided better degree of personal protection than the candles [181]. A commercial repellent Bite Blocker™ provided protection up to 7.2 and 3.5 hours under laboratory and field conditions, respectively, against *Ae. aegypti*, *Ae. canadensis*, *Ae. eudes* and *Ae. fitchii* [182, 183]. Essential oils of *Cinnamomum camphora*, *C. cassia* and *C. zeylanicum* showed repellent action against several species of mosquitoes [184, 185].

5.4.2.2. Repellent Activity on other Haematphagous Arthropods

Essential oils obtained from *Eucalyptus* produced high repellency against the human head louse, *P. humanus capitis* [186]. Essential oils from *E. cinerea*, *E. viminalis* and *E. saligna* showed KT_{50} values of 12.0, 14.9 and 17.4 min, respectively against permethrin-resistant human head lice [187]. A lemon eucalyptus extract from *E. maculata citriodon* showed good repellent activity against mosquitoes, midges, ticks and stable flies [188-190]. Essential oils from *Pogostemon cablin* provided protection up to 3.7 hours against *S. calcitrans*. Very strong repellency was also produced by *Eugenia caryophyllata*, *Levisticum officinale* (3.2-3. 5 h) and *Thymus vulgaris* (2.1 h) against this species [191]. Essential oils of *Melaleuca ericifolia* effectively repelled bush fly *Musca vetustissima* and the biting midges *Culicoides ornatus* and *C. immaculatus* [192]. Thavara *et al.* examining repellency in cockroaches reported that essential oils from *Citrus hystrix* led to 100% repellency against *Periplaneta americana* and *Blattella germanica* and 88% against *Neostylopyga rhombifolia* under laboratory conditions [193] *Citrus hystrix* formulated as 20% active ingredient in ethanol, exhibited 86% reduction in *P. americana* and *N. rhombifolia* populations under field conditions. Essential oils from catmint, *Nepeta cataria* at 15% active ingredient conferred complete protection for 7.5 h from *Simulium decorum* under field conditions [194]. Eucalyptol from eucalyptus oil showed fumigant activity against first-instar nymphs of the bloodsucking bug *Rhodnius prolixus,* a vector of Chagas disease, yielding KT_{50} value of 216 min as compared to 30 minutes for dichlorvos [195].

Essential oils have been shown to have repellency for numerous non-insect arthropods including ticks and chiggers. Those from *Amyris balsamifera* and *Maclura pomifera* effectively repelled the blacklegged tick, *Ixodes scapularis*, and the lone star tick, *Amblyomma americanum* up to 4 hours [192]. Essential oils from *Syzygium aromaticum* exhibited 100% repellency against host-seeking chiggers, *Leptotrombidium imphalum* (a vector of scrub typhus), at a 5% concentration [196]. Essential oils from citronella, cloves and lily of the valley repelled *Ix. ricinus* to the same magnitude as DEET [197]. Whereas, essential oils of *Melaleuca alternifolia, Zingiber cassamunar* and *Eu. globules* exhibited 100% repellency against *L. imphalum* at concentrations ranging from 40 to 100% [196]. Thyme oil at 0.14 mg oil cm^{-3} effectively repelled the poultry mite, *Dermanyssus gallinae* up to 13 days [198]. Essential oils obtained from *Eucalyptus* produced high repellency against the *Ixodes* tick [199].

5.4.3. Ovicidal Activity

Besides toxic and repellent properties, essential oils have been shown to have a pronounced effect on the developmental period, growth, adult emergence, fecundity, fertility and egg hatching of insects [95, 200]. Hexane extract of *Andrographis lineat, A. paniculata* and *Tagetes erecta* showed 100% ovicidal activity against *An. subpictus* [200]. Essential oils from *Juniperus macropoda* and *Pimpinella anisum*, *Zingiber officinale* and *Rosmarinus officinalis* showed strong ovicidal properties against *Ae. aegypti, An, stephensi*, and *Cx. quinquefasciatus* [186]. Essential oils of *Piper guineense* and *Xylopia aethiopica* deterred oviposition by gravid female *Ae. aegypti* for up to 48 hours [201]. Essential oils from *Aglalia, Alpinia, Curcuma, Eleutherococcus, Hedychium, Houttuynia, Litsea, Manglietia, Melaleuca, Murraya, Myristica, Ocimum, Piper, Psidium, Schefflera, Vitrex,* and *Zingiber* plants exhibited 16.6 to 94.7% oviposition deterrence against *Ae. aegypti* [202]. Rosemary oil, pulegone, thymol, and eugenol showed up to 100% oviposition deterrent activity against *Ae. aegypti* [175]. One μL of linalool and 10.0 μL of pine oil completely inhibited oviposition by house flies [203]. While piperitenone oxide isolated from *M. spicata viridis* completely inhibited *An. stephensi* oviposition at 75.0 g ml^{-1} dosage. Female adults exposed to the essential oils of this species laid 42-fold fewer eggs at the dose of 60.0 g ml^{-1} as compared with an untreated control [176].

5.4.4. Growth Regulating Activity

Eessential oils have been reported to have a pronounced effect on the developmental period, growth, and adult emergence [95, 198]. Exposure of insect vectors to active botanical derivatives can affect result in an extension of the duration of development [95]. It is estimated that over one thousand plant species contain bioactive substance that act as IGRs [204]. Examples of such IGR's include ajugarins isolated from *Ajuga remora* [205]. Crushed aqueous extract of *Opuntia tuna, Callistemon lanceolatus, Clerodendron incrme* and *Lantana camara* severely affected *Cx. quinquefasciatus* molting and metamorphosis by interfering in production of larval-to-larval, larval-to-pupal, pupal-to-adult intermediates, and supernumerary molts besides causing ecdysial failure and mortality [206].

5.4.5. Multiple Activities

Several essential oils or their constituents have been reported to possess multiple activities (insecticidal, repellent, ovicidal and growth inhibition properties) [56, 207]. For examples, Neem oil has been shown to act as larvicide, oviposition inhibitor and growth regulator, against *Cx quinquefasciatus*, *An. culicifacies, An. stephensi,* and *Ae. aegypti* [56, 207]. Rosemary oil, pulegone, thymol and eugenol showed both larvicidal and ovicidal activity against *Ae. aegypti* [157]. Essential oils from *A. indica, Z. zerumbet, D. biflorus and M. pudica* showed larvicide, adulticide and repellent activities against *Cx. gelidus* and *Cx. quinquefasciatus* [106]. Flower extract and essential oils of *Tagetes minuta* showed adulticide, larvicide and repellent activity against *Ae. aegypti, An. stephensi* and *Cx. quinquefasciatus* [207]. Pine oil and linalool isolated from pine oil completely suppressed *M. domestica* feeding and oviposition up to 24 hrs [203]. Prajapati *et al.* evaluated 10 essential oils extracted from medicinal plants for larvicidal, adulticidal, ovicidal, oviposition-deterrent and repellent activities against *An. stephensi, Ae. aegypti* and *Cx. quinquefasciatus* [184]. Essential oils extracted from *Zingiber officinale* and *Rosmarinus officinalis* showed both ovicidal and repellent activities, whereas essential oils from *Cinnamomum zeylanicum* exhibited strong repellent and oviposition-deterrent activity against these species. Essential oils of *Juniperus macropoda* and *Pimpinella anisum* showed both larvicidal and ovicidal activity against *An. stephensi* and *Ae. aegypti*. Essential oils from *Cinnamomum camphora, Allium cepa, Matricaria piperita, M. chamomilla* killed 100% of adult buffalo lice, *Haematopinus tuberculatus* within two minutes under laboratory conditions. These oils also showed ovicidal properties against this species and protected buffaloes from *M. domestica, S. calcitrans, Haematobia irritans* and *Hippobosca equine* flies for up to 6 days [164]. Piperitenone oxide isolated from *Mentha spicata viridis* showed larvicidal, ovicidal, developmental toxicity, and repellent properties against larval and adult *An. stephensi* [158]. Butler patented 77 plant and animal based compounds that showed attractants or repellent of which 29 showed insecticidal activities against *Ae. aegypti, Ae. albopictus, An. quadrimaculatus, M. domestica,* or *S. calcitrans* [176]. Constituents of essential oils such as Beta damascene, citronellol, geranyl acetone, and rosalva showed insecticidal activity against several insect species including *Ae. aegypti, Ae. albopictus, An. quadrimaculatus, M. domestica,* and *S. calcitrans* and *Lutzomyia shannoni* [93,94]. Celangulin isolated from *Celasutrus angulatus* showed gastrointestinal toxicity, antifeedant activity, contact toxicity, and inhibition of growth and development in *Ae. albopictus* [208].

5.4.6. Synergistic Activity

As with toxicity, the effect of a phytochemical on the inhibition of insect vector growth and reproductive capacity is governed by insect species, plant species, plant parts, concentration and type of solvents used in an extraction. Most studies on the synergistic, antagonistic and additive toxic effects of binary mixtures involving phytochemicals have been conducted on agricultural pests rather than pests of medical importance [95]. The mosquitocidal activity of binary mixes has been reviewed by Shaalan *et al.* [95]. *Zanthoxylum piperitum* + 5% vanillin provided better protection against *Ae. gardnerii, An. barbirostris, Armigeres subalbatus, Cx. tritaeniorhynchus, Cx. gelidus,* the *Cx. vishnui* group, and *Mansonia uniformis* than *Z. piperitum* or vanillin alone or 25% DEET [209]. The addition of piperonyl butoxide significantly (3-250-fold) increased larvicidal activity of pulegone, thymol, eugenol, trans-anithole, and citronellal and rosemary oil against *Ae. aegypti* [157]. Citronella oil, in concentrations ranging from 0.05% to 15% increased efficiency of cedarwood, lavender, peppermint, clove, garlic and eucalyptus oil against *Ae. aegypti* [175]. Similarly the essential oils from *Blumea lacera* synergized pyrethrum activity [209]. An increase in the protection time was produced when essential oils from *Eugenia caryophyllata, Levisticum officinale* and *Thymus vulgaris* (3.2-3. 5 h) were mixed with *Calophyllum inophyllum* oil producing protection times comparable to the most widely used synthetic repellent DEET [191]. The addition of 5% of vanillin in *Eu. globulus* oil improved the protection time against *Ae. albopictus* [210]. Whereas, addition of vanillin to *Zanthoxylum piperitum* essential oils had a repellant effect with DEET-tolerant *Armigeres subal-*

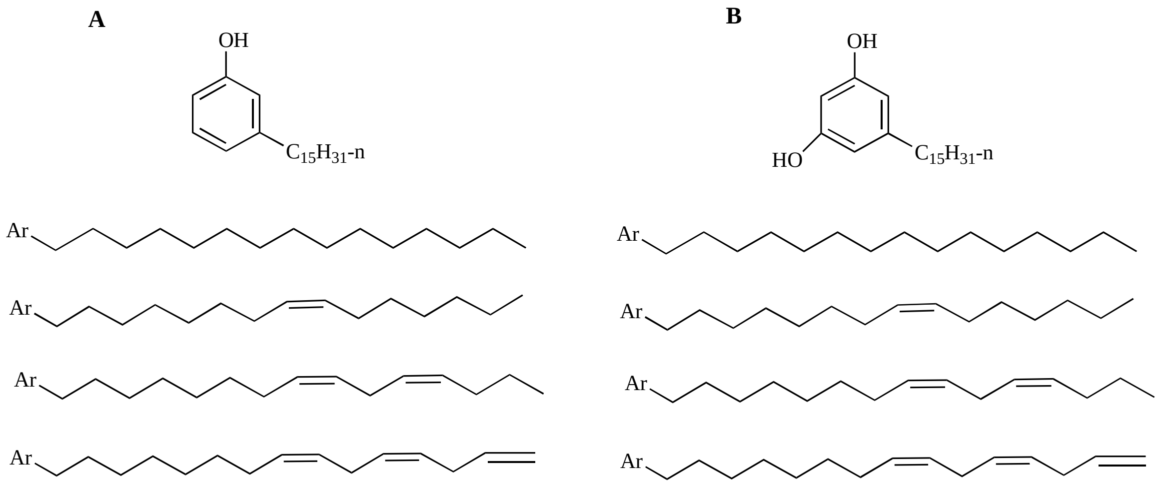


Fig. (6). Structures of cardanol (**A**), cardol (**B**).

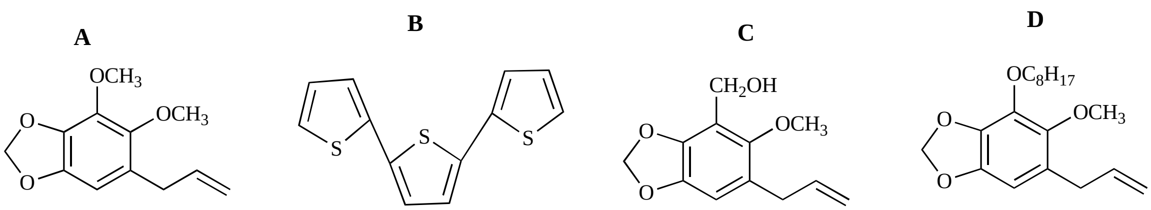


Fig. (7). Structures of dillapiol (**A**), alpha-terthienyl (**B**), replacement of methoxy group of dillapiol with hydroxylmethyl group (**C**), replacement of methoxy group of dillapiol with long chain octyloxy group (**D**).

batus mosquitoes [209]. Shallan *et al.* argued that a less active natural pesticide could possess exceptional synergistic qualities in combination with other synthetic or natural insecticidal agents. Furthermore, joint-action of natural pesticides and synthetic pesticides might enhance control activities and minimize the development of insecticide resistance [95].

5.4.7. Structure-Activity Relationships

Terpenes and other low molecular weight aromatic compounds such as alcohols, ketones, aldehydes, and carboxylic acid constitute the primary ingredients of essential oils, which determine the biological properties of the essential oils [13, 68]. Within terpenes, monoterpenes are the most representative molecules constituting 90% of the essential oils; however, hemiterpenes, sesquiterpenes, diterpenes, triterpenes and tetraterpenes are also components of these essential oils [68]. The toxicity of these oils is often associated with the presence of one or more volatile mono-terpenoids. Some monoterpenes, such as α-pinene, 1,8-cineole, eugenol, limonene, terpinolene, citronellol, citronellal, camphor and thymol, are the most common constituents of a number of essential oils providing toxic or repellent activity (113, 186, 211, 212). Lucia *et al.* reported that toxicity of *Eucalyptus* essential oils against *Ae. aegypti* was directly proportional to concentration of the monoterpene *p*-cymene in the essential oils. However the toxicity was reduced by higher concentrations of the monoterpene 1,8-cineole [131, 213].

Although toxic, repellent or oviposition deterrent properties of essential oils are primarily associated with the presence of monoterpenoids and sesquiterpenes, presence of other constituents such as alcohols, ketones and aldehydes have also been reported to attribute towards activity of essential oils against arthropods [15, 94, 214]. Phytol, a linear diterpene alcohol, has high repellent activity against *An. gambiae* as compared to other alcohol, aldehyde or carboxylic components of essential oils [94, 214]. Furthermore, the structure–toxicity relationships between these constituents also have been reported to influence potency of natural compounds [215-217]. Rice and Coats working on the effect of several natural pesticides on house flies suggested that shape, degree of saturation, carbon skeleton, volatility and type of functional group could have a significant influence on cuticle penetration, thereby affecting the ability of the compounds to move and interact with their active sites [215]. Lomonaco *et al.* and Laurens *et al.* reported that hydrogenation of double bonds in cardanol (Fig. **6A**) and cardol (Fig. **6B**) isolated from *Anacardium occidentale* resulted in decreased larvicidal activities against *Ae. aegypti* [216, 218].

Belzile *et al.* found that when the allyl side chain of dillapiol (Fig. **7A**) was modified, its synergistic activity with alpha-terthienyl (Fig. **7B**) was either reduced or eliminated against *Ae. atropalpus* [219]. Replacement of the methoxy group with hydroxylmethyl group (Fig. **7C**) led to smaller synergism factors between alpha-terthienyl and dillapiol while exchanging the methoxy group by the long chain octyloxy group (Fig. **7D**) had essentially no effect.

Santos *et al.* reported that the stereochemistry of compounds plays an important role on modulating the potency of compounds against different insects. Structurally related R-carvone and S-carvone (Fig. **8**) compounds exhibited different potency profiles on *Ae. aegypti* with LC_{50} values varying from 124 to 154 mg L^{-1} [217].

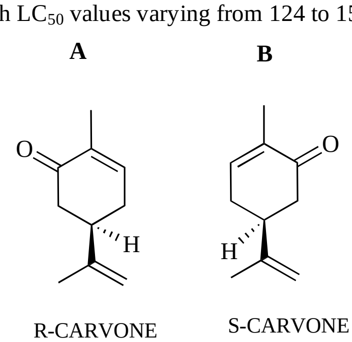


Fig. (8). Structures of S-carvone (A), R-carvone (B).

Shifting the exo double bond in limonene (Fig. **9A**) resulted in nearly two fold less potent ɣ-terpinene (Fig. **9B**). Lack of double bond in limonene along with the presence of a three membered ring, resulted in the bicyclic compound 3-carene (Fig. **9C**) with five times lower in potency [217, 220]. Furthermore, addition of heteroatoms to the cyclic hydrocarbon structure of limonene resulted in an overall decrease in potency.

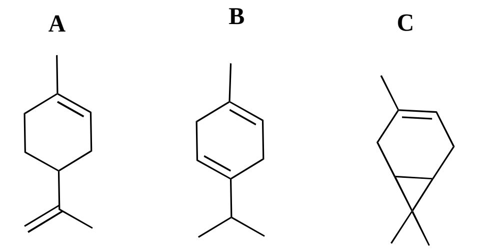


Fig. (9). Structures of limonene (A), γ-terpinene (B), 3-carene (C).

Aliphatic compounds, camphene, camphor, bornel, and isoborneol (Fig. **10A**) exhibited lower potency than the aromatic compounds, carvacrol, eugenol, p-cymene and thymol (Fig. **10B**). Presence of lipophilic group in the aromatic ring resulted in increased potency of terpenes against *Ae. aegypti*, whereas presence of hydroxyl group in the aromatic ring resulted in decreased potency. Removal of the hydroxyl group from both aromatic and aliphatic compounds resulted in increased potency, whereas addition of hydroxyl group resulted in less potent compounds [217]. The authors suggested that increased number of hydroxyl groups may prevent the penetration of the compounds in the larval cuticle thus reducing potency of compounds with more hydroxyl groups than the compounds with fewer hydroxyl groups. An additional hydroxyl in the meta position of phenol in thymol resulting in resorcinol produced in more than two-fold decrease of potency. Similar to the aromatic subset, the addition of hydroxyls to aliphatic compounds resulted in less potent compounds [217]. Similar results were also reported by Waliwitiya *et al.* showing that aromatic compounds (thymol, and eugenol) exhibited better larvicidal activities than the aliphatic compounds (camphene and camphor) against *Ae. aegypti* [156]. Ngoh *et al.* reported that benzene derivative, eugenol were more toxic or repellent to *P. americana* than the terpenes, cineole [74]. Nerio *et al.* suggested that the type of carbon where the hydroxyl substitution is present modulates repellency of essential oils against mosquitoes [166].

However, insect response could not be predicted solely on the basis of molecular structure. The authors evaluated 38 compounds belonging to terpene, alcohols, ketones and carboxylic esters against *Ae. aegypti* and *An. quadrimaculatus* and found that LC_{50} and LC_{90} values showed wide variations within the terpenes, alcohols, ketones and carboxylic esters. Furthermore, structural isomers, such as geraniol and nerol (Fig. **11A**), within the terpene alcohols, and between *α*-damascone and *δ*-damascone (Fig. **11B**) within the ketones showed different toxicities. Similar response variation was also observed within the carboxylic ester isomers methyl jasmonate and methyl dihydrojasmonate (Fig. **10C**) evaluated against these same species [15]. However, variations in LC_{50} and LC_{90} values were not related to carbon skeleton, position or number of double bonds. These findings were supported by Mann *et al.* in *S. calcitrans* and *M. domestica* [93].

6. SAFETY TO HUMANS AND ENVIRONMENT

After identification and isolation of viable natural pesticides that aggressively suppress target pest populations, the next step is the evaluation of these compounds for safety to humans and other non-target organisms. Although natural pesticides are the lesser of many hazards, in terms of general pesticide toxicities, they are toxins nonetheless, and all toxins used in pest control pose some hazard to the user and the environment [221]. However, only limited information is available on safety of these chemicals to humans and other animals despite their large scale use in the flavor and fragrance industry [221-223]. Ames and Gold reported that almost half of the tested natural plant produced toxins are carcinogenic under high dosages in rodents [224]. Essential oils isolated from the Australian species *Dacrydium franklini* and *Melaleuca bracteata*, can cause skin irritation [225]. A monoterpenoid d-limonene has been shown to be nephrotoxic in male rats [226] and to have immunosuppressive effects in mice [227]. Pure essential oils of carvacrol and pulegone has low acute oral LD_{50} values of 2-3 g kg^{-1} against rats. Neem, thymol and α-terpeniol have 4.0, 6.6 and 16.1 mg kg^{-1} LC_{50} values, respectively, against rainbow trout in static water tests [228]. Variable results have been reported for neem formulations and extracts ranging from no effect to significant effects on non-target organisms. Rao *et al.* found no significant effects of neem formulations on aquatic insects, frog tadpoles, and plant spiders when evaluated against *Culicine* and *Anopheline* larvae in rice fields [65]. However, Kreutzweiser reported that neem pesticides were toxic to *Isonychia bicolor* (mayfly) [229]. Similarly, rotenone causes death in fish inhibits the electron transport chain induces hepatocyte apoptosis, and induces Parkinson's disease [230-234]. Some natural pyrethrin insecticides are as neurotoxic as synthetic pyrethroids [235]. Lindberg *et al*. reported that Magic3™ a mixture of 5 essential oils was toxic to honey bees [236]. Therefore, it should be recognized that natural pesticides or their derivatives are not free of risk and require further field investigations. However, in some parts of the world, the risks of arthropod transmitted disease are far greater than risks originating from natural pesticides [237].

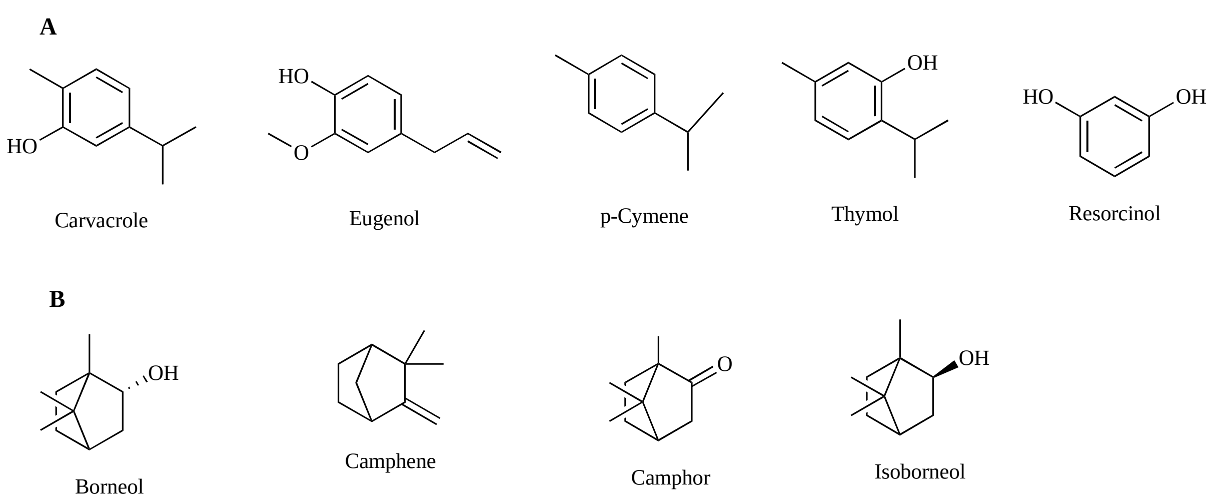


Fig. (10). Structures of aliphatic compounds (**A**), aromatic compounds (**B**).

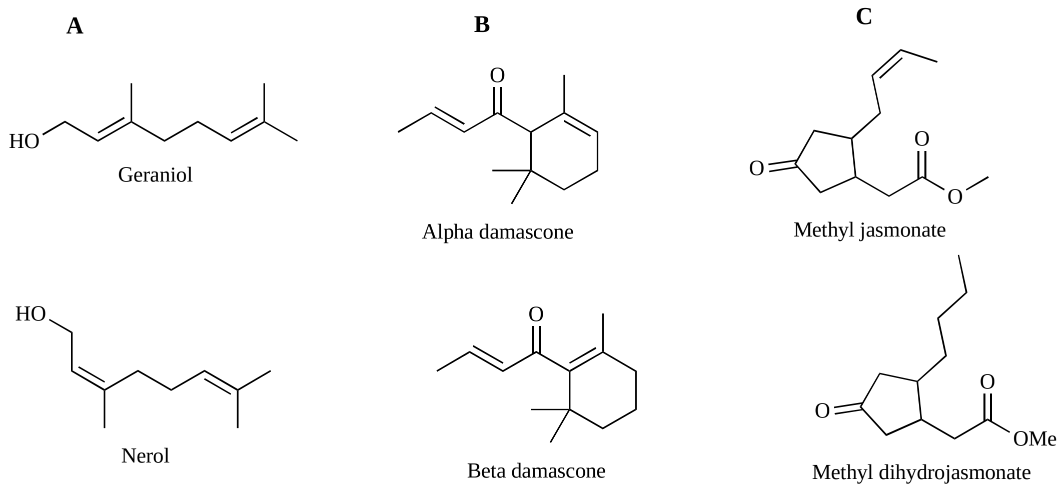


Fig. (11). Structure of terpene alcohols (**A**), ketones, (**B**), carboxylic ester (**C**).

7. DELIVERY METHODS

Once the natural pesticides are isolated and confirmed for biological activity, the next step is development of appropriate formulations to deliver the product at minimum cost without loss in quality. The formulated product should effectively suppress pests in the field with rapidity, be adequately stable under prolonged environmental conditions to produce extended pest control and have sufficient safety and patentability to be registered and allowed to market for commercialization [95]. Since technical insecticides are rarely used and formulation can significantly affect control efficacy, various formulations must be tested to enhance stability, reduce human toxicity, improve efficacy or facilitate handling of the product. As with crop chemicals, natural pesticides must be economical to produce, have persistent storage stability and adequate field persistence, be easy to handle, mix, and apply, and provide consistently effective control of the target pest or group of pests. Natural pesticides can be formulated as both conventional liquid (aqueous and non-aqueous solutions or dispersions) and solid (wettable powders and water-dispersible granules) systems or as controlled-release systems.

The choice of formulation is influenced by several factors, such as the physical, chemical, and biological properties of the pesticide; the mode of application; the commodity or area to be treated; and current agricultural practices [13]. Moretti *et al.* showed that encapsulation process is a suitable method for entrapping essential oils of very different chemical compositions to produce high-loaded microparticles that offer protection against environmental agents and loss of the active ingredients [238]. In addition, these formulations offer the possibility of controlled release rates of active ingredients. Microcapsules and polymer systems can provide continuous, long-term release of active ingredients. In these formulations the active ingredient is contained in tiny capsules produced by coacervation, interfacial polymerization, extrusion and other processes. The release rate of the active ingredients is determined by the size and number of capsules, composition and thickness of the capsule walls, the concentration and properties of the active ingredient and other additives used [239]. Several new companies are developing aerosol and dust formulations containing proprietary mixtures of essential oils compounds for controlling domestic pests (cockroaches, ants, fleas, flies, wasps, etc.). Most insect repellents are effective in vapor phase therefore; volatility, temperature, humidity and wind enhance evaporation affecting the longevity of the repellents [239, 240]. High vapor pressure repellents may repel the vectors at low dosages as compared to low vapor pressure repellents [239]. Commercial insect repellents are available in multiple formulations including aerosol and pump sprays, lotions, creams, gels, controlled release formulations, camouflage face paint, clothing treatments, and towelettes. For example, dlimonene is an active ingredient in commercially available flea shampoos [13]. A flea collar for pet dogs was manufactured by adding essential oils (Eucalyptus, Cedarwood, Citronella and Peppermint) to ethylene-vinyl acetate polymer in a mixture [241].

Slow release formulations have been developed and marketed recently. It was shown that film-forming formulations and use of carboset acrylic polymers were extremely effective in improving the efficiency of DEET in military mosquito control programs [242]. A controlled release polymer formulation of Ultrathion™ 3M containing a 33% DEET base performed significantly better than did a 71% DEET in ethanol formulation against *An. flavirostris* [239]. New developments in spatial repellent technology have led to development of technologies that repel the vectors at a set distance from the repellent molecule source [239]. Therma CELL® repellent technology consisting of butane-fueled generator with a heated metal plate to evaporate allethrin from an impregnated pad effectively repelled mosquitoes and sand flies up to a distance of 7 m for 6 hrs. Currently, commercialization of such products is limited to synthetic chemicals only. However, it is expected that discovery and commercialization of highly effective natural products will provide an impetus to the development of improved formulations for natural pesticides.

8. FUTURE OF NATURAL PESTICIDES AGAINST INSECT VECTORS

Plant extracts possess a wide range of biological activities. Production of plant based toxins is a result of coevolution of plant species with microorganisms and herbivores. Thus, secondary compounds from plants are highly active against arthropods. However, isolation and chemical characterization of the active compounds from plants with strong biological activities can be a tedious, inexact process compared to synthesizing new synthetic compounds. Natural compounds are generally isolated in relatively small amounts compared to the predictable production of synthesized chemicals, making availability for screening a challenge. Therefore, initial bioassays are limited to very small amounts of compounds. After promising biological activity is discovered analogues of the compound might be considered by chemical alteration and/or chemical synthesis. Structural manipulation could lead to improvement of activity, toxicological properties, altered environmental effects, or discovery of an active compound that can be economically synthesized [19]. This has been the case with several natural compounds that have been used as a template for commercial pesticides, including the most widely used pesticides, synthetic pyrethroids [19, 243].

Isman identified three barriers to the commercialization of new products (i) the scarcity of the natural resource; (ii) the need for chemical standardization and quality control; and (iii) difficulties in registration. Regulatory approval remains the most formidable barrier to the commercialization of new insecticides. However, the advances in chemical and biological technologies combined with increasing need and environmental pressure, are greatly increasing the interest in plant products as pesticides. However, it will be necessary to develop focused coordinated research and education programs to develop cost effective and standardized extraction methods, bioassay techniques, safety evaluation procedures, appropriate and efficacious formulations, increased stability and shelf life, proper packaging and labeling, and streamlined registration and labeling procedures to promote and accelerate the use of natural pesticides in vector management programs.

ABBREVIATIONS

LC_{50}: Lethal concentration	=	Concentration required to kill 50% of a test population.
LC_{90}: Lethal concentration	=	Concentration required to kill 90% of a test population.

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None declared.

CONFLICT OF INTEREST

None declared.

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