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Volatile phytochemicals as mosquito semiochemicals

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Abstract

Plant biochemical processes result in the release of an array of volatile chemical substances into the environment, some of which are known to play important plant fitness enhancing functions, such as attracting pollinators, thermal tolerance of photosynthesis, and defense against herbivores. Cunningly, phytophagous insects have evolved mechanisms to utilize these volatiles to their own advantage, either to colonize a suitable host for feeding, reproduction and oviposition or avoid an unsuitable one. The volatile compounds involved in plant–insect chemical interactions have been widely exploited in the management of agricultural pests. On the other hand, use of plant volatiles in the management of medically important insects is limited, mainly due to paucity of information on their role in disease vector–plant interactions. To date, a total of 29 plant volatile compounds from various chemical classes, including phenols, aldehydes, alcohols, ketones and terpenes, have been identified as mosquito semiochemicals. In this review, we present highlights of mosquito–plant interactions, the available evidence of nectar feeding, with particular emphasis on sources of plant attractants, methods of plant volatile collection and the candidate plant volatile compounds that attract mosquitoes to nectar sources. We also highlight the potential application of these phytochemical attractants in integrated mosquito management.

Keywords

Plant–insect interactions; Phytochemicals; Semiochemicals; Attractants; Mosquitoes; Disease vectors

1. Introduction

Plants synthesize and emit a wide range of volatile organic compounds including terpenoids, fatty-acid derivatives, benzenoids, nitrogen containing compounds and other scented substances (Knudsen et al., 1993). These compounds serve a variety of functions for the plants such as pollinator attraction, direct and indirect self-defense against herbivores, and for their own metabolic processes (Paré and Tumlinson, 1999; Berkov et al., 2000; Schiestl et al., 2000; Loreto and Velikova, 2001; Schiestl and Ayasse, 2001; Sharkey et al., 2001; Van Poecke et al., 2001). In an evolutionary arms race, herbivorous insects have adapted mechanisms to identify suitable host plants and to evade non-host plants using their floral scents (Visser, 1986). These plant–insect interactions that involve volatile chemical

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communication have been widely exploited in the management of agricultural pests. However, their use in the management of medically important insects, such as mosquitoes, remains largely unexplored.

Several studies on plant–mosquito interactions have shown that floral nectar forms an important component of both male and female mosquito diet. Among these, are the mosquito species *Anopheles*, *Culex* and *Aedes* that transmit diseases such as malaria, yellow fever, dengue fever, West Nile virus, Rift Valley fever, chikungunya, St. Louis encephalitis, and lymphatic filariasis to man and his livestock. Reisen et al. (1986) showed that 75% females and 68% males of field collected *Culex tarsalis* tested positive for fructose, indicating that plant nectar feeding constituted a normal diet of this mosquito species. Similar results were obtained from field collected *Aedes albopictus* in coastal Israel (Müller et al., 2010c). In mosquitoes collected in western Kenya, Beier (1996) demonstrated that 6.3% of the indoor-resting and 14.4% of host-seeking *An. gambiae* s.l. and *An. funestus* tested positive for fructose. Several other studies have documented evidence of facultative or obligate nectar feeding of mosquitoes in nature (Foster, 1995; Stone and Foster, 2013).

Sugar feeding has been identified as essential in mosquito energetic budget. While only females mosquitoes feed on vertebrate blood for gonotrophic development, both sexes of all ages and gonotrophic stages require sugar meals, derived from plant sources for important processes such as flight, metabolism and fecundity (Nayar and Sauerman, 1971; Magnarelli, 1977, 1978; Van Handel and Day, 1988; Manda et al., 2007). In addition, the excessive growth of fat body and elevation of lipid reserves that are associated with adult diapauses have been linked to a boost in sugar feeding accompanied with up regulation of fatty acid synthase genes in some mosquito species such as *Culex pipiens* (Jaenson and Ameneshewa, 1991; Bowen, 1992a; Robich and Denlinger, 2005; Sim and Denlinger, 2009). Sugar feeding has been shown to continue throughout diapause in *Culex tarsalis* during mild winters (Reisen et al., 1986). Furthermore, newly emerged females of small size have been shown to require an initial sugar or blood meal to develop their follicles to stage II before undergoing vitellogenesis and egg maturation (Lounibos and Conn, 1991; Briegel and Horler, 1993). Sugar also plays an important role in the early stages of adult development and, in nature, the availability and abundance of sugar sources determine the frequency of sugar feeding (Van Handel et al., 1994; Martinez-Ibarra et al., 1997; Gu et al., 2011).

In this review, we highlight on some of the sources of attractive plant compounds that likely direct mosquitoes to a sugar meal, the various volatile collection techniques that have been employed in these studies, as well as their advantages and disadvantages, and identities of the plant compounds attractive to mosquitoes. We also give an insight into the prospects for deployment of plant volatile compounds in surveillance and control of disease transmitting mosquitoes.

2. Sources of attractive plant odours

The potential for plant volatiles to lure mosquitoes has been known since the 1960s with the observation by Sandholm and Price (1962) that various mosquitoes species in the field were attracted to light-coloured flowers with distinct fragrances. Almost two decades later, the individual contributing roles of visual and olfactory cues in mosquito attraction was established for *Anopheles arabiensis* Patton and *Aedes aegypti* Linnaeus (Healy and Jepson, 1988; Jepson and Healy, 1988). In separate studies using a wind tunnel designed to evaluate long range attraction of mosquitoes, Jepson and Healy demonstrated an upwind flight and landing of these two mosquito species to the inflorescences of *Achillea millefolium* and *Leucanthemum vulgare* respectively both in the presence and absence of visual cues. Prior to these studies, Joseph (1970) trapped various species of *Aedes*, *Culex*, *Anopheles*, *Psorophora*, and *Culiseta* mosquitoes using damaged and over ripe apples, grapes, peaches and water-melons in the field. The attractiveness of flowers and fruits/pods to wild mosquitoes has also been demonstrated for *An. gambiae* (Müller et al., 2010b) and *Aedes albopictus* (Müller et al., 2011). Laboratory assays have further shown that floral and vegetative scents play a vital role in the attraction of *Ae. aegypti* to *Asclepias syriaca* (Vargo and Foster, 1982), *Culex pipiens pipiens* to *L. vulgare*, *A. millefolium*, *Asclepias syriaca*, and *Solidago canadensis* (Mauer and Rowley, 1999; Otienoburu et al., 2012), and *An. gambiae* to *Parthenium hysterophorus*, *Ricinus communis* and *Bidens pilosa* (Nyasembe et al., 2012).

Plant scents emanate from both the floral and vegetative parts (Knudsen et al., 1993; Pichersky and Gershenzon, 2002). These plant scents are synthesized either *in situ* and stored in glandular trichomes or *de novo* when plants are under attack by herbivores (Jakobsen and Olsen, 1994; Paré and Tumlinson, 1997). While plant scents has been well established for the floral parts, in particular for pollinator attraction, similar studies on the vegetative parts are continuously being explored because of their complexity and functions they play (Knudsen et al., 1993). The general plant volatiles are those formed *via* biosynthetic pathways common in most plants. These include fatty acid derivatives from unsaturated fatty acids formed through lipooxygenase pathway (Kunst and Samuels, 2003) and terpenoids through melanovate and methylerythritol phosphate pathways (Lichtenthaler et al., 1997; Eisenreich et al., 1998). Besides fatty acids, plant volatiles contain terpenes, which constitute the largest and most structurally diverse group of compounds (Degenhardt et al., 2009). Specific volatile components arise from further modification of these secondary metabolites through reduction or removal of carboxyl groups, addition of hydroxyl groups, or formation of esters and ethers catalyzed by various enzyme families (Dudareva et al., 2004). The fruit aroma consists of a complex mixture of compounds including terpenes, esters, aldehydes and alcohol, and sulphur-based compounds among others, the biosynthesis of which is regulated by ethylene (Sanz et al., 1996; Lalel et al., 2003).

3. Volatile collection techniques

With the realization of the significance of plant volatile organic compounds in plant–insect interactions, there has been a growing interest in the chemistry, biochemistry, physiology, and ecology of these compounds. This has led to the development of a variety of techniques for the collection and analysis of plant volatiles (Harborne, 1998; Millar and Sims, 1998). The choice of the most suitable system for collection of plant volatiles is dependent on the biological problem and the plant material being investigated (Tholl et al., 2006). Several volatile collection and analysis techniques have been used in identifying various mosquito attractive compounds (Table 1).

Solvent extraction has been widely used to collect plant volatiles for elucidation of their potential attractiveness to various mosquito species, with a single solvent (Otienoburu et al., 2012) or a series of solvents (Vargo and Foster, 1982; Jepson and Healy, 1988) used to extract floral compounds of different plant species. Solvent extraction is advantageous in that it is possible to get the full volatile organic profile of the plant by varying the type of solvent used. However, this method suffers a major limitation in that it does not give a realistic picture of the actual volatile compounds emitted by plants that are likely to play key ecological roles in plant–insect interactions. Furthermore, this method is liable to contamination by impurities present in the solvent.

Another method that has been employed collecting volatiles from mosquito host plants is the static headspace volatile collection techniques (Otienoburu et al., 2012). In their study, Otienoburu et al. (2012) placed *Asclepias syriaca* florets in a glass vial and collected the volatiles on solid phase micro-extraction (SPME) fibre with no circulation of air. Various SPME fibres that adsorb volatile organic compounds of varying polarity and molecular weights are available and have been reviewed in Tholl et al. (2006). The amount of compounds collected depends on the thickness of the fibre coating and the distribution constant of the analyte. This method is advantageous in sampling volatile organic compounds from low emitting plants and eliminates the need for solvents which might introduce impurities. The major disadvantage of this method is that it does not allow for repeated injection of the sample, quantification is not possible when dealing with a wide range of compounds with different distribution constants, and accumulation of humidity, heat and deleterious chemicals which might interfere with the physiology of the plant (Tholl et al., 2006).

Healy and Jepson (1988) used dynamic headspace volatile collection technique in which they placed freshly cut inflorescences of *Achillea millefolium* in a glass jar and passed charcoal filtered air over the inflorescences through adsorbent matrix (activated charcoal). Similar method was used by Jhumur et al. (2007, 2008) and Nyasembe et al. (2012) to collect volatiles from flowers on to adsorbent Tenax-TA and Carbotrap and from intact plants on to Super-Q traps respectively. However, both studies by Healy and Jepson (1988) and Jhumur et al. (2007, 2008) used a ‘closed-loop stripping’ system while Nyasembe et al. (2012) used a ‘push–pull’ system. In the former system, volatiles were collected through continuous circulation of headspace air inside closed chambers, while in the later air was pulled over the plant sample through an adsorbent trap connected to a vacuum pump.

Overall, the dynamic headspace volatile collection has several advantages including providing sufficient amount of volatiles for detection and structure elucidation, no increase in temperature and humidity and reduced accumulation of deleterious chemicals in the headspace (Tholl et al., 2006). However, this volatile collection method is limited by incomplete adsorption of volatile organic compounds due to different trapping matrices having specific affinities for volatile organic compounds. For instance, activated charcoal is less efficient in trapping aromatic aldehydes, while Tenax-TA and Super-Q have low affinity for low molecular weight or polar compounds. This often calls for combination of two or more of the adsorbent matrices to increase the range of volatile organic compounds trapped. For instance, Jhumur et al. (2007, 2008) used both Tenax-TA (high affinity for lipophilic to medium polar organic compounds) and Carbotrap (wide range of organic compounds but with easy decomposition of terpenes).

4. Plant volatiles detected by mosquitoes

Volatile compounds emitted by plants vary greatly, and their activity on various insect species depends on their quality and quantity and the recipient insect species. Several plant compounds have been identified as responsible for host plant location by foraging mosquitoes (Table 1). Pioneer studies aimed at identifying antennally active plant compounds relied on antennal sensilla recordings to synthetic plant compounds. Notable was the study carried out by Lacher (1967) who demonstrated antennal sensilla response to terpenes in *Ae. aegypti*. Further evidence of mosquito antennal response to plant-related odours was demonstrated in *Ae. aegypti* and *Ae. triseriatus* which were shown to respond to *o*-cresol (**1**, Fig. 1) and related compounds (Davis, 1976; Bentley et al., 1982). Using *Cx. pipiens*, Bowen (1992b) discovered a high proportion of both broadly- and narrowly-tuned antennal receptor neurons sensitive to a group of terpenes (thujone **2**, verbenone **3**, α-pinene **4**, citral **5**, nerol **6**, limonene **7**, and farnesol **8**, Fig. 1), green leaf volatiles (hexanal **9**, 1-hexenol **10**, and (*Z*)-3-hexen-1-ol **11**, Fig. 1) and fatty acid esters (ethyl propanoate **12**, methyl propanoate **13**, ethyl butyrate **14** and ethyl acetate **15**) (Fig. 1). However, behavioural assays with thujone, the major constituent, only elicited a close-range dose-dependent probing response in *Cx. pipiens* but did not stimulate upwind flight in a wind-tunnel olfactometer. Although these studies did not conclusively demonstrate behavioural activity of the identified compounds, they served as a foundation for more elaborate studies into the involvement of chemical cues in plant –mosquito interactions.

Several years later, the advancement of more refined volatile entrainment and analytical techniques that allow characterization of the full profile of plant volatiles have seen more mosquito attractive plant compounds identified. Jhumur et al. (2007) demonstrated antennal responses of *Cx. pipiens* and *Ae. aegypti* to twelve compounds of *Silene otite* inflorescences including phenylethyl alcohol **16**, phenylacetaldehyde **17**, lilac aldehydes **18**, (*Z*)-3-hexenyl acetate **19**, linalool oxide **20**, linalool **21**, benzaldehyde **22**, lilac alcohol **23**, acetophenone **24**, methyl salicylate **25** and hexanal **9** (Fig. 2). Of these, linalool oxide, linalool and hexenyl acetate elicited the strongest antennal response (Jhumur et al., 2008). Only four compounds *viz.* acetophenone, linalool oxide, phenylacetaldehyde, and phenylethyl alcohol elicited significant behavioural response in *Cx. pipiens* in olfactometer assays. The attraction of *Cx. pipiens* to *Asclepias syriaca* (Asclepiadaceae) has also been attributed to three major constituents of the floral scent; phenylacetaldehyde **17**, benzaldehyde **22** and (*E*)-2-nonenal **26** (Fig. 2) (Otienoburu et al., 2012). In our previous study (Nyasembe et al., 2012), we demonstrated electrophysiological and behavioural activity of the malaria vector *An. gambiae*, to six plant compounds identified from *P. hysterophorus*, *R. communis* and *B. pilosa*. These included hexanal, limonene, (*Z*)- and (*E*)-linalool oxide, β-pinene **27**, (*Z*)- and (*E*)-β-ocimene **28**, and (*E*)-β-farnesene **29** (Fig. 2).

Some of these plant compounds have previously been shown to play a role in insect–plant interactions. For instance, (*E*)-β-farnesene and (*E*)-linalool oxide have been shown to elicit electrophysiological and behavioural responses in the western flower thrips, *Frankliniella* *occidentalis*, while phenylacetaldehyde has been shown to be attractive to the cabbage butterfly, *Pieris rapae*, and the cotton bollworm, *Helicoverpa armigera* (Honda et al., 1998; Agelopoulos et al., 1999; Bruce and Cork, 2001). Linalool oxide, lilac aldehydes and lilac alcohol are isomers derived from oxidation of linalool. These isomers have been associated with the fragrance of various plants and have been shown to elicit electrophysiological activity in the noctuid moth, *Hadena bicruris*, which is known to rely on lilac aldehydes to locate its host plants (Dötterl et al., 2006). Their detection by various mosquito species highlights the significance of this group of plant compounds in insect–plant interactions. Overall, the coincidence in detection of identical volatile compounds from different plant species by different insect species supports the argument that it is the qualitative and quantitative composition of plant compounds rather than the presence of a certain individual compound that imparts specific sensory impression on insects (Najar-Rodriguez et al., 2010). Most plants have a common biosynthetic pathway resulting in release of similar groups of compounds but of varying proportions (Schwab et al., 2008), hence it is not surprising that insects have evolved a way of utilizing different combinations of plant volatiles to locate a suitable host. Careful cellular screening of these compounds can reveal their bioactivity in mosquito vectors and the knowledge generated combined with molecular understanding employed in developing better management tools for these disease vectors.

Plant-derived volatiles are important for many nectar feeding and herbivorous insects which associate them with particular plant species, with many relying on specific blends of these compounds for identifying the particular plant species exploited as feeding or oviposition sites (Pichersky and Gershenzon, 2002; Bruce et al., 2005; Bruce and Pickett, 2011). Varied semiochemicals play important roles in host-plant location by insects which can vary in structural and chemical complexity in different habitats (Bruce et al., 2005; Najar-Rodriguez et al., 2010; Gols et al., 2012). The list of attractive volatile chemicals identified from different mosquito host plants vary considerably, and although some of these compounds may be common across the plant species, the ratios in which they are released is important (Visser, 1986; Bruce et al., 2005). The success of any insect–resource interaction is dependent on the ability of the insect to successfully locate the resource. Therefore, the observed variations could possibly indicate an adaptive or innate evolution on the part of various mosquito species to identify their potential host plants using specific or general cues and their proportions to locate potential nectar sources.

Variation in plant volatile emission among different plant species and even within the same species but in different geographical locations has been reported (Knudsen, 2002; Jhumur et al., 2008). Although the evolutionary significance of this variability in mosquito–plant interactions is not known, genetic drift or natural selection may account for such differences (Tollsten and Bergström, 2008).

5. Potential application of phytochemicals in mosquito vector management

Effective control of disease vectors often depends on several complementary approaches that combine to form an integrated vector management strategy. Despite many years of concerted efforts to control vector-borne diseases, the burden associated with these diseases still remains unacceptably high (The malERA Consultative Group on Monitoring, 2011). Of particular concern includes malaria and arboviral diseases transmitted by various mosquito species. This has prompted the need to develop new control strategies with the exploitation of vector ecology seen as a viable target for new and more environmentally friendly control tools (Ferguson et al., 2010; Govella and Ferguson, 2012). In addition to application as general toxicants against immature mosquitoes, phytochemicals may also have potential uses as repellents, larvicidal, ovicidal and oviposition deterrents, growth and reproduction inhibitors as well as attractants (Rajkumar and Jebanesan, 2005; Pushpanathan et al., 2006; Foster, 2008; Stone and Foster, 2013).

Recent advances in the knowledge of chemical mediation in mosquito–plant interactions presents a unique opportunity for development of new vector control tools. Unlike vertebrate host odour baited traps which target mainly blood seeking female mosquitoes, traps baited with plant volatile compounds have the potential of attracting both male and female mosquitoes of diverse age groups and varying gonotrophic stages (Foster, 2008). Besides their potential for deployment as attractive lures for surveillance of mosquito population, phytochemical attractants can also be used in mass trapping in control operations. This would particularly add more arsenal to vector control strategies with the recent discovery of outdoor biting fractions of *An. gambiae* which has sustained the transmission of malaria even in communities where use of insecticide treated bed nets is high (Riehle et al., 2011; Zhou et al., 2011).

Studies have shown that spraying of vegetations around water bodies with attractive toxic sugar baits can reduce mosquito populations by up to 98% (Schlein and Müller, 2008; Müller et al., 2010a; Beier et al., 2012). Furthermore, knowledge of the semiochemicals mediating mosquito–plant interaction can be utilized in luring mosquitoes into traps baited with highly selective insecticides or entomopathogenic agents such as fungi and viruses. The potential of this approach in integrated vector management is exemplified in *Culex quinquefasciatus* oviposition pheromone ((*5R,6S*)-acetoxy-5-hexadecanolide) which when combined with the insect growth regulator pyriproxifen resulted in increased oviposition accompanied by killing of the emerging larvae (Agelopoulos et al., 1999; Mboera et al., 2000).

Furthermore, advances in the biochemical pathways of semiochemical production, perception and processing as well as molecular characterization of odour receptors in mosquitoes should open avenues for molecular approaches that promise to spearhead a new wave of research to establish the role of semiochemicals in the future of integrated vector management (Renwick, 2009). Efforts to identify mosquito odour binding proteins for both vertebrate and plant hosts would provide a starting point for the potential use of odour binding proteins as targets to interfere with mosquito host location (Zhou et al., 2010). Such non-insecticidal approaches could play an important role as part of integrated vector management strategies and broaden the arsenal of available tools for disease vector control.

It is however worth noting that semiochemicals alone might not be sufficient as a control tool against mosquitoes, but their use can be maximized through integration with other existing mosquito vector control strategies which can provide a powerful tool that can help reduce and even eliminate vector populations.

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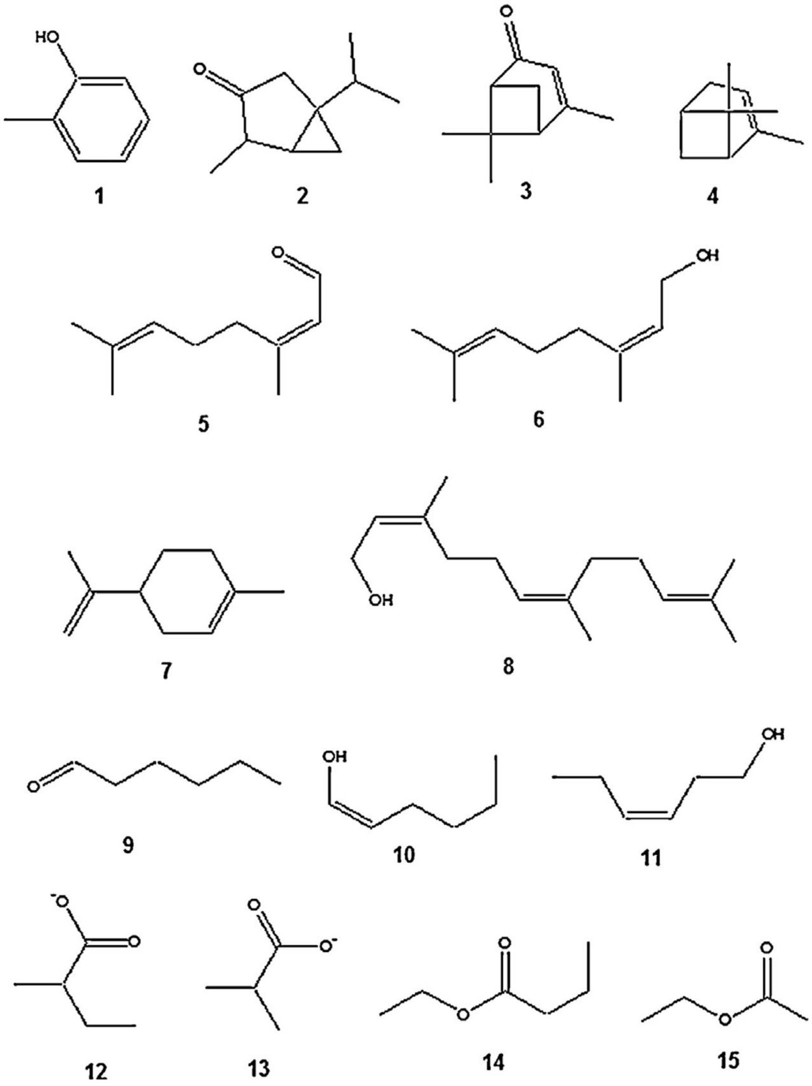

Fig. 1.

Structures of electrophysiologically-active phytochemicals for mosquitoes. They include *o*-cresol **1**, thujone **2**, verbenone **3**, α-pinene **4**, citral **5**, nerol **6**, limonene **7**, and farnesol **8**, hexanal **9**, 1-hexenol **10**, and (*Z*)-3-hexen-1-ol **11**, ethyl propanoate **12**, methyl propanoate **13**, ethyl butyrate **14**, and ethyl acetate **15**.

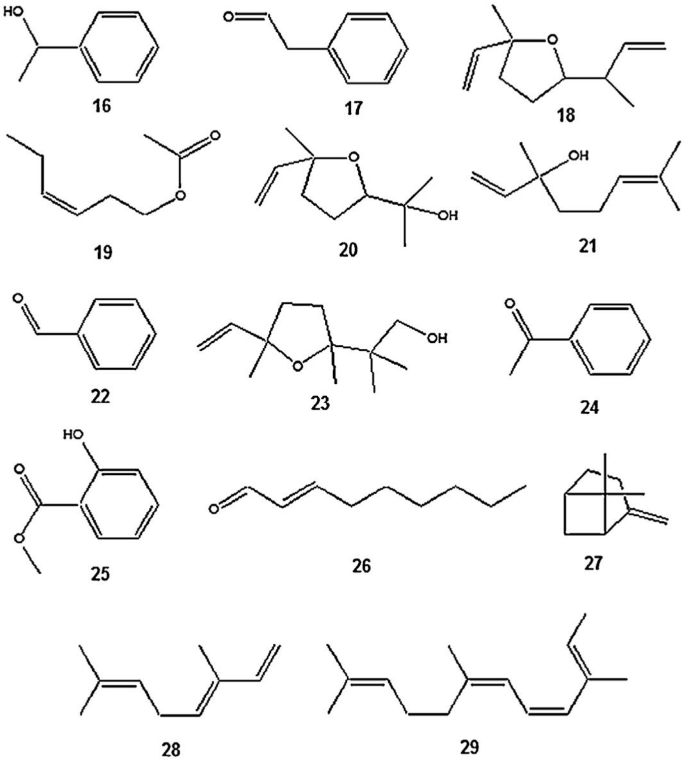

Fig. 2.
Structures of electrophysiologically- and behaviourally-active phytochemicals for mosquitoes. They include phenylethyl alcohol **16**, phenylacetaldehyde **17**, lilac aldehydes **18**, (*Z*)-3-hexenyl acetate **19**, linalool oxide **20**, linalool **21**, benzaldehyde **22**, lilac alcohol **23**, acetophenone **24**, methyl salicyilate **25**, (*E*)-2-nonenal **26**, β-pinene **27**, (*Z*)- and (*E*)-β-ocimene **28**, and (*E*)-β-farnesene **29**.

Table 1

Chemical analysis of mosquito attractive plant compounds: source, plant part, methods of volatile collection and analysis and the identified compounds.

Source	Targeted mosquito species	Plant part	Volatile collection method	Method of analysis	Compounds identified	References
Synthetic standards	*Ae. aegypti*	–	–	Single sensilla recording	Terpeniol, geraniol, eugenol, citral, citronellol and fatty acids	Lacher (1967)
Synthetic standards	*Ae. aegypti*	–	–	Single sensilla recording	Geraniol, eugenol, amyl acetate, toluene	Davis (1977)
A. millefolium	*An. arabiensis*	Flowers	Dynamic headspace air entrainment, activated charcoal, pentane	GC-MS	Cyclic and bicyclic monoterpene	Healy and Jepson (1988)
Synthetic standards	*Cx. pipiens*	–	–	Single sensilla recording	Thujone, verbenone, α-pinene, citral, nerol, limonene, and farnesol, hexanal, 1-hexenol, and (*Z*)-3-hexen-1-ol, ethyl propanoate, methyl propanoate, ethyl butyrate and ethyl acetate	Bowen (1992b)
S. otites	*Cx. pipiens molestus* and *Ae. aegypti*	Flowers	Dynamic headspace, Tenax-TA and Carbotrap tube, acetone	GC-EAD and GC-MS	Phenylethyl alcohol, phenylacetaldehyde, lilac aldehydes, (*Z*)-3-hexenyl acetate, linalool oxide, linalool, benzaldehyde, lilac alcohol, acetophenone, methyl salicylate and hexanal, 1-hexenol, Z-3-Hexen-1-ol	Jhumur et al. (2007, 2008)
A. syriaca	*Cx. pipiens*	Flowers	Solvent extraction in pentane and static headspace, DVB/CAR/PDMS SPME fibre	GC-MS	Phenylacetaldehyde, benzaldehyde and (*E*)-2-nonenal	Otienoburu et al. (2012)
P. hysterophorus, R. communis, B. pilosa	*An. gambiae*	Intact plant	Dynamic headspace, Super-Q, dichloromethane	GC-EAD and GC-MS	Hexanal, limonene, (*Z*)-and (*E*)-linalool oxide, β-pinene, (*Z*)-and (*E*)-β-ocimene, and (*E*)-β-farnesene	Nyasembe et al. (2012)

GC-EAD = gas chromatography-electroantennography, DVB/CAR/PDMS = divinylbenzene/carboxen/polydimethylsiloxane, SPME = solid phase micro-extraction.