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Excito-repellency and biological safety of β-caryophyllene oxide against *Aedes albopictus* and *Anopheles dirus* (Diptera: Culicidae)

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ABSTRACT

The activity of β-caryophyllene oxide as either a contact or noncontact repellent was evaluated against two laboratory strains (*Aedes albopictus* and *Anopheles dirus*) using an excito-repellency test system. *N, N*-Diethyl-3-methylbenzamide (DEET) was used as a standard reference baseline for comparative purposes. β-Caryophyllene oxide and DEET were tested at concentrations of 0.1, 0.25, 0.5 and 1.0% (v/v). In addition, the phototoxic and genotoxic effects of β-caryophyllene oxide were investigated on Balb/c 3T3 mouse fibroblasts (3T3-L1) and Chinese hamster ovary cell line (CHO-K1). The results demonstrated that the higher concentrations of test compounds (0.5 and 1.0%) produced greater behavioral responses. *Aedes albopictus* was more sensitive to β-caryophyllene oxide than *An. dirus*. Moderate avoidance response rates (25-56% escape) of *Ae. albopictus* at 0.5% and 1.0% β-caryophyllene oxide were observed in contact and noncontact trials compared with low response rates from *An. dirus* (26-31% escape). DEET at $\leq 1\%$ displayed lower irritancy and repellency (1-38%) than β-caryophyllene oxide when tested against the two mosquito species. Knockdown responses (37%) were only observed in *An. dirus* exposed to 1% β-caryophyllene oxide in the contact trial. β-Caryophyllene oxide did not show any phototoxic potential (PIF = 0.38) nor was there any significant genotoxic response as indicated by no increase in micro-nucleated cells with or without metabolic activation. β-Caryophyllene oxide could be considered as a safe repellent, effective against mosquitoes.

1. Introduction

Mosquito-borne diseases represent a key hazard for millions of people worldwide. Mosquitoes serve as vectors of pathogens for devastating human scourge, including malaria, filariasis, yellow fever, dengue, West Nile virus and chikungunya (Benelli and Mehlhorn, 2018). Malaria and dengue are the two most common mosquito-borne diseases that cause high morbidity and mortality (Wiwanitkit, 2011). Millions of humans in the least developed and developing countries are mainly at risk from these diseases. To a lower extent, now developed countries are too at risk of dengue outbreaks due to the invasion of *Aedes albopictus* (Skuse) into temperate regions and population movement from dengue-endemic areas (Vairo et al., 2018). In 2017, an estimated 219 million cases of malaria occurred worldwide, with an estimated 435,000 deaths from malaria globally (WHO, 2018).

Anopheles dirus Peyton & Harrison is the most important malaria vector in Southeast Asia (Tainchum et al., 2015). This species inhabits forest and forest fringes and exhibits mostly exophagic behavior (Baimai et al., 1984; Tananchai et al., 2012, 2019). In contrast, dengue and chikungunya are arboviral infections transmitted by two species of *Aedes* mosquitoes—*Aedes aegypti* L. and *Ae. albopictus*. The latter, known as the Asian tiger mosquito, is native from Southeast Asian countries (Smith, 1956). The distribution of *Ae. albopictus* has been extended recently by invasion into more northerly latitudes as well as into higher altitudes such as the United States of America and Europe (Chouin-Carneiro et al., 2016; Martinet et al., 2019). These two mosquito species have been found highly refractory to common control tools due to their highly exophagic behavior and are regarded as great potential vectors even though they are present in low population densities. Therefore, the prevention and control of most vector-borne

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