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Review article

Botanical essential oils and uses as mosquitocides and repellents against dengue

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ABSTRACT

Plants naturally produce bioactive compounds along with many secondary metabolites which serve as defensive chemical against herbivorers including insect pests. One group of these phytochemicals are the 'Essential Oils' (EO's), which possess an extensive range of biological activity especially insecticidal and insect repellents. This review provides a comprehensive viewpoint on potential modes of action of biosafety plant derived Essential Oils (EO's) along with their principal chemical derivatives against larvae and adult mosquito vectors of dengue virus. The development and use of Essential Oils (EO's) effectively applied in small rural communities provides an enormous potential for low cost effective management of insect vectors of human pathogens which cause disease.

1. Introduction

Dengue is among the most pervasive mosquito-borne viral diseases in the world (Benelli and Mehlhorn, 2016; Benelli, 2015a, 2015b). In the past decade, the occurrence of this disease has amplified 30-fold. Over one hundred endemic countries with around 2.5 billion people were infected with the dengue virus (WHO, 2014; Pavela, 2015). Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF) are triggered by the different types of four dengue viral serotypes (DEN 1, 2, 3 and 4) which are closely linked to antigenically. To the infection with one serotype delivers ultimate protection to that host virus only, but not to the others. Dengue disease viruses are spread in metropolitan cities especially in tropical and subtropical areas by the disease mosquito vector of *Aedes aegypti* (L.), a species closely linked with human residences (WHO, 2012). Reported estimates are almost 100 million cases per annum occur (Guzman and Harris, 2015; Christofferson, 2015). Thus, *Ae. aegypti* is regarded as the principal vector of this virus in India (WHO, 2009). Conversely *Ae. albopictus* (Skuse) (the tiger mosquito) also an important vector whose geographic range has greatly expanded within the past 20 years and is considered a major vector of viral pathogens being second only to *Ae. aegypti* (Waldock et al., 2013; Wilkerson et al., 2015). Rates of transmission and spread vary greatly among the four dengue serotypes (Christofferson, 2015). Regrettably, there are no effective medicines against dengue virus infections from the four virus serotypes (Dias and Moraes, 2014).

World Health Organization (WHO) considers dengue vector control as one of the most important actions to reduce the spread of disease. The chief implement in the management of the mosquito vectors is the application of chemical pesticides such as organochlorine, organophosphate and pyrethroid compounds. Unfortunately success is low due to human behaviors, scientific, preparation inconsistencies, development of resistance, and high cost-factors (Ghosh et al., 2012). Compounding the urgency for an effective treatment is the development of insecticide resistance among mosquito populations (Senthil-Nathan et al., 2004, 2005; Pates and Curtis, 2005; Thanigaivel et al., 2012, 2017). Overuse and misuse for many decades of synthetic insecticides with various formulations have occurred since the 1960's with Temephos, an organophosphates being applied across many countries (Braga et al., 2004; Silva et al., 2004, 2008). Resistance development is further encouraged by frequent applications of commercial insecticides without proper rotation (Tan et al., 2014; Erland et al., 2015). Due to rapid development of chemical resistance in mosquito population's and high costs of synthetic insecticides, researchers have focused on developing alternative methods and chemicals to reduce dengue vectors (Rodriguez

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et al., 2002; Macoris et al., 2003; Silva et al., 2008). Thus these efforts have expanded the need to categorize novel mosquitocidal agents and their specific modes of action in order to increase development of effective treatments, while maintaining human safety (Shaalan et al., 2005; Govindarajan et al., 2013; Dias and Moraes, 2014; Senthil-Nathan et al., 2006a, 2006b; Senthil-Nathan, 2007, 2015). International organizations like WHO (2005) also had elevated expanding the use of botanical phytochemicals as a critical need, wherein they issued a "…Guidelines for Laboratory and Field Testing of Mosquito Larvicides". These guidelines outline the importance and requirement for derived phytochemicals to be evaluated for efficacy by comparison to currently used chemical insecticides.

Botanical derivatives have gained renewed interest and examination as a resource for unique chemistries with activity against mosquito vectors (Senthil-Nathan et al., 2008a, 2008b; Gahukar, 2012; Senthil-Nathan, 2013; Ponsankar et al., 2016b). Plants are the equivalent of 'natural industrial chemical factories' which produce a wide range of common and unique phytochemicals such as steroids, terpenoids, alkaloids, phenolics, Essential Oils (EOs) extracted from plants is one of the most common low cost products which is widely used as an alternative to commercialized synthetic insecticides (Shaalan et al., 2005; Gbolade and Lockwood, 2008; Govindarajan, 2010; Gleiser et al., 2011; Ghosh et al., 2012; Giatropoulos et al., 2013; Gokulakrishnan et al., 2013; Soonwera, 2015; Soonwera and Phasomkusolsi, 2016; Bedini et al., 2016; Govindarajan et al., 2015, 2016c, d). EOs are considered to be safer phytochemicals due to a long history of use for human consumption, fragrances, and medicines for thousands of years (Cheng et al., 2003; Shaalan et al., 2005; Govindarajan et al., 2013). Major plant families like, Asteraceae and Solanaceae, contain members: Cladophoraceae, Cupressaceae, Labiatae, Lamiaceae, Oocystaceae, Miliaceae, Rutaceae, Poaceae, Zingeberaceae and Piperaceae have been shown to have extracts with mosquitocidal activities against different species of mosquito vectors (Shaalan et al., 2005; Amer and Mehlhorn, 2006a, 2006b; Bakkali et al., 2008; Silva et al., 2008; Cheng et al., 2009a, 2013; Nerio et al., 2010; Kalaivani et al., 2012; Rehman et al., 2014; Pavela, 2015; Govindarajan et al., 2013, 2016a, 2016b, 2016c, 2016d; Baskar et al., 2016).

EOs include a mix of many phytochemicals and often contain > 60 compounds (Bakkali et al., 2008; Liu et al., 2013; Rehman et al., 2014; Ellse and Wall, 2014). Extraction methods to produce EO products from plants include; flowers, seeds, roots, bark, and leaves, includes soaking in water or steam distillation, expression under pressure, solvent extractions (such as ethanol) (Baskar et al., 2016) and subcritical water extractions (Edris, 2007). More modern methods of EO extraction include a microwave-assisted process and supercritical liquid extraction process (Regnault-Roger et al., 2012; Pavela, 2015). Some of the best known EOs derived from plants have been commercially marketed (Choochote et al., 2007), this includes products from Neem trees, *Azirdiractin indica* (Baskar et al., 2016). Despite the wide use of EOs in vector control across developing nations, it is important to increase the understanding of their specific mode of actions to also improve their use in mosquito vector management. This review is to establish a foundation from the scientific literature filtered with keywords like 'Essential Oils against dengue vector' 'larvicidal activity', 'repellent activity' from the major databases: Science Direct, Pub Med and other biological and scientific abstracts. A list assembled from the literature search covers the last five years Supplemental reference Tables 1, 2 and 3.

2. EOs as Larvicides

Strategies which target developmental stages of insect vector, aim to stop the emergence of adult insects which are the active 'transporter' or vector of the pathogen causing harm. Thus this has been proposed to be a critical strategy in the control dengue vectors and for reducing the spread of disease pathogens (Chung et al., 2009). Traditionally there are various methods for controlling larvae which are achieved through chemical, cultural and biological means separately or as components of a larger integrated pest management (IPM) strategy. Alteration of the larval environment, draining all standing water, introduction of fish or other aquatic predators, and covering water containers are a few examples of these components (Knio et al., 2008). Insecticide applications to manage adult *Ae. aegypti* populations include Temephos, Fenthion, Malathion, Deltamethrin, and Permethrin (Biber et al., 2006; David et al., 2014; Diniz et al., 2015). Currently, the uses of biological agents against mosquito larvae have successfully decreased the incidence of dengue by reducing the emergence of mosquito adults (Marcombe et al., 2012). Increased use of EOs against different mosquito dengue vectors follow reports that the LC_{50} value can be very low, with reports of efficacy using < 100 ppm (Cheng et al., 2009a, b). Formulations of EOs in products like PONNEEM a novel herbal formulation from neem and karanj oil have show prominent larvicidal activity more so than on mosquito adults (Maheswaran and Ignacimuthu, 2012). Pohlit et al. (2011) reported that Asian countries especially China, Japan, Korea and India are the primary countries submitting patents for EO products many of which are used against dengue vectors (Cheng et al., 2013). The majority of isolated EOs are isolated from the whole plant or more frequently leaves (Table 1. Larvicides). An extensive review on EO larvicides was conducted by Dias and Moraes (2014) which reported on 361 EO preparations. From these 269 plant species were evaluated for mosquitocidal toxicity. More than 60% of these were considered active at an LC50 < 100 mg/L when tested on *Ae. aegypti* larvae. The majority of these EOs were prepared from medicinal plant species within the Myrtaceae, Lamiaceae, and Rutaceae, with EO extracted from seeds (80%) having the highest larvicidal activity. While leaves were extracted more often the larvicidal activity was only 50%. Reviews of larvicidal potential of EOs with their effective constituents against the dengue mosquito vectors and development of new alternatives for dengue vector control can be found in: (Autran et al., 2009; Dias and Moraes, 2014; Kishore et al., 2014).

3. Phytochemicals of EOs

Phytochemical characterizations of EOs are classified into two different chemical groups based on the metabolic pathway used for synthesis: 1) terpenoids. The terpenoids are primarily the monoterpenes and less common the sesquiterpenes; and 2) phenylpropanoids (Dias and Moraes, 2014; Pavela and Benelli, 2016). Monoterpenes (10-carbon) are biosynthesized in plastids whereas; sesquiterpenes (15-carbon) are synthesized in the cytosol. The monoterpenes are formed through methylerythritol phosphate pathway whereas, and sesquiterpenes are twisted through the mevalonate pathway. Monoterpenes were forms unique cyclases structures of acyclic, monocyclic and bicyclic. Sesquiterpenes have a diverse range of structures with > 100 skeletons, the 15 carbons increases the elongation of the chain which increases the possible number of cyclizations formed in the cytosol (Regnault-Roger et al., 2012). Monoterpenes are considered to be the most representative chemicals with > 90% composition of EOs (Pavela, 2015). However, chemical composition is highly diverse from one species to another, with variation sometimes even within a single species. The variation is because the expressions of phytochemicals in a plant are diverse and changing at all stages through development (Regnault-Roger et al., 2012). Alterations of phytochemicals also occur post production being modified for new functions or for storage (Santos et al., 2014). One example of these changes are the EO isolated from *Majorana hortensis* Moench (mint family Lamiaceace) which displays differences in their chemical compositions when they were stored in light or dark conditions (Misharina et al., 2003). The chief constituents of monoterpenes includes: alcohols, aldehydes, carbures, ketones, ethers, esters, peroxides, phenols and lactones. The major phytochemicals of the above said groups includes; α-pinene, menthol, linalool, carvone, camphor, eucalyptol, thujone, myrcene, thymol, cineole, ascaridole, and nepetalactone etc… (Pavela and Benelli, 2016). Pavela