A Review on the Potential and Efficacy of Plant-Based Mosquito Repellents Against DEET-Based Mosquito Repellents

Andrea Ysobel T. Bacolor, Jenmond Alphine V. Guno, Dominic Kyle S. Rodriguez, Paula Justine F. Santos, and Eula Kathrina M. Tizon
De La Salle University Integrated School, Manila

Abstract: The number of insect-borne diseases has brought many health-related issues, prompting the search, discovery, and formulation of insect repellents to prevent the acquisition of diseases. However, the preferred and conventional chemical-based repellent has downsides contrary to the benefits, such as the concern towards human and environmental safety. Meanwhile, scientific understanding of plants is mainly underexplored, resulting in people's preferences for chemical-based insect repellents. The main objective of this review was to evaluate the efficacy of N, N-diethyl-3-methyl-benzamide (DEET), found in chemical-based repellents, and terpenes, found in plant essential oil-based repellents, to show the potential of both, along with the possibility of using plant-based repellents as an alternative to the conventional ones. The review was done by comparing and analyzing the fundamental data obtained from previous studies, focusing on the DEET or essential oil concentration, repellency rate, protection time for the efficacy, and the mosquito species that the tested repellents have shown to repel. After reviewing and comparing the results from primary sources, the researchers concluded that DEET-based and plant-based repellents both have potential depending on the concentration and the process of repellent formulation, as some plant-based repellents demonstrate longer protection times and thus greater potential than some of the DEET-based ones.

Key Words: DEET; terpenes; mosquito repellent; repellent-active compounds; efficacy

1. INTRODUCTION

1.1. Background of the Study

Blood-sucking and disease-carrying insects are a major cause of illness to children and adults worldwide, especially in tropical and subtropical climates (Family Doctor, 2017). This prompted the search and formulation of repellents that contain the ingredient N, N-diethyl-3-methyl-benzamide (DEET) to prevent such insect-borne diseases. While DEET repellents are proven to be the most preferred and widely used (Moore et al., 2018), there are human safety and environmental concerns along with its use. High concentrations (10% or more) being needed for the application to be effective can produce adverse effects such as dermal reactions, neurotoxic and cardiotoxic effects, seizures, or convulsions (Legeay et al., 2018). DEET has also been detected in wastewater, surface water, and groundwater (Gao et al., 2020). Moreover, studies have shown that these conventional repellents can already be resisted by Aedes aegypti (Almadiy, 2020). Thus, it is significant to search for repellent alternatives that do not include hazardous chemicals and instead take on safer and natural ingredients that pose fewer risks, such as those derived from plant extracts. Although plants as repellents have potential and are already moderately used, the scientific understanding of these plants is underexplored. This review looks more into plant-based repellents, evaluates their efficacy, and compares them to those of chemical-based repellents.

1.2. Research Objectives

To be able to evaluate and compare the efficacy of chemical-based and plant-based mosquito repellents with the active compounds present, the researchers did the following:
research published articles dating from 2016 to 2021;
determine the properties of active compounds of both chemical-based and plant-based repellents;
compare and evaluate significant similarities and

differences in the efficacy of DEET and essential oils with terpenes as mosquito repellents; and
conclude the potential of plant-based repellents as an alternative to chemical-based repellents.

1.3. Scope and Limitations

The scope of this review is the evaluation of the potential of chemical repellents based on DEET and natural repellents based on plant essential oils (EOs) containing terpenes. This review covered various studies that measured the repellent activity of the said compounds against mosquito species of the order Diptera. With the reported data from previous studies, the present study is only in the form of a written review. A conclusion regarding the potential of plant-based repellents and chemical-based repellents was formulated only through the obtained information from the gathered studies.

1.4. Significance of the Study

The study serves as an exploration and evaluation of plant-based and chemical-based repellents through their efficacy. Through this, the study imparts knowledge to the general public by providing information and conclusions about the potential of the conventional chemical-based repellents and the natural repellents that are accessible and environmentally friendly. It contributes to the awareness of communities in tropical and subtropical areas regarding the advantage and usefulness of phytochemicals from plants to control insects. On a larger scale, this could contribute to the production of chemical-based and plant-based repellents, as a broader understanding of the two is essential for future innovations.

2. METHODOLOGY

2.1 Subsection

Give the support for your main claim by showing evidence for it. What are the foundations of your claim (theoretical framework)? What conclusion/s follow from it. How are you deriving the conclusion from the basis/bases of your claim (methodology)? It is not always necessary to actually state the specific logical rules for your inferences. It depends on the style that you are taking on in writing your paper. (In papers that are not highly analytical, if you find it necessary to label the actual process/es of derivation of your conclusion, do it in the footnotes.) But the correct inference must be made apparent here and you have to convince your audience of your argument.

Figures and tables should be referred to in the text. They should be centered as shown below and must be of good resolution.

2. Review of Related Literature

2.1. Active Compounds

2.1.1. Chemical-Based N, N-diethyl-3-methyl-benzamide

Chemical compounds are often used in the formulation of commercially available repellent products. Figure 1 shows the chemical structure of one of the most widely used synthetic chemicals, N, N-diethyl-3-methyl-benzamide, commonly known as DEET.

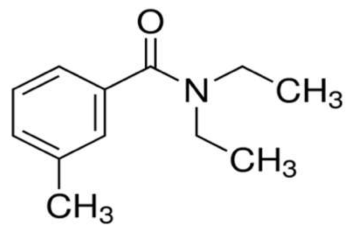


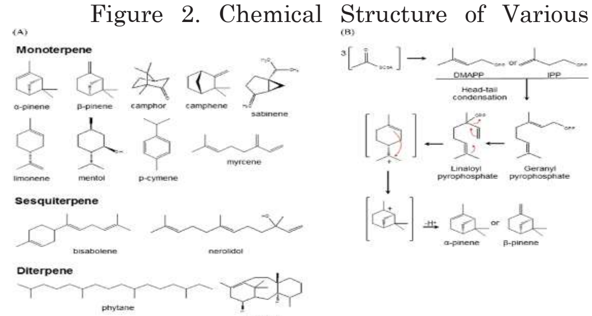
Figure 1. Chemical Structure of N, N-diethyl-3-methyl-benzamide

DEET is known to be the 'gold standard' for repellents for its long-lasting repellency towards different species of arthropods such as mosquitoes, ticks, fleas, and flies. DEET-based repellents are available worldwide today in various formulations, including aerosols, creams, lotions, sprays, gels, sticks, and wipes (towelettes) at concentrations ranging from 5% to 100% (Riffell, 2019).

2.1.2. Plant-Based Terpenes

Among the classes of plant secondary metabolites, terpenes is the largest and most diverse group. As shown in Figure 2, terpenes are composed of branched 5-carbon isoprene units assembled in different ways and are thus classified according to the number of isoprene units they contain (Ali, 2020; Ramirez-Gomez et al., 2019). These lipid-soluble compounds are synthesized by all organisms through the mevalonate and deoxy-D-xylulose pathways (Sahebi et al., 2017).

Figure 2. Chemical Structure of Various



Terpenes

Monoterpenes, which consist of two isoprene units, are important components of plant EOs. Limonene, linalool, linalyl acetate, citronellal, and carvone are some of the monoterpenes (Hussein & El-Anssary, 2018). Terpenes and terpenoids being constituents of most EOs, allow them to act as insect repellents (Ali, 2020; Valduga et al., 2019).

2.2. Study Designs and Methods

2.2.1. Gas Chromatography-Mass Spectrometry

Gas chromatography-mass spectrometry (GC-MS) is the method used to identify and quantify the active constituents in the extracted EOs from plants. The identification of the chemical components and the calculation of their corresponding percentage compositions are done as the peaks of the chromatographs are compared with the library (Arpiwi et al., 2020; Manh & Tuyet, 2020).

2.2.2. Nanoemulsion and Microencapsulation Processes for Repellent Formulations

Mohammadi et al. (2019) used the process of nanoemulsion for the formulation of some plant-based repellents. Nanoemulsion is the two-phase dispersion of two immiscible liquids, either water in oil or oil in water droplets which are stabilized by an amphiphilic surfactant (Singh et al., 2017). Moreover, Misni et al. (2016) utilized microencapsulation to formulate some repellent lotions tested against Ae. aegypti. Microencapsulation is a method used particularly in commercial repellent formulations, wherein the EO is encapsulated by a natural or synthetic polymeric membrane for it to control the release rate and prevent the volatile compounds from evaporating (Beestman 2003, Tuetun et al., 2008, as cited in Misni et al., 2016).

2.2.3. Repellency Test

The arm-in-cage method is a measurement test of efficacy for topical mosquito repellents under laboratory conditions. In this method, starved female mosquitoes are contained in the test cage where the skin impregnated with the repellent is exposed. The repellent is applied to the forearm area while a glove contours the unexposed part to prohibit the mosquitoes from biting there (Colucci & Müller, 2018). Mohammadi et al. (2019), Manh and Tuyet (2020), Misni et al. (2016), and Arpiwi et al. (2020) used this method based on the WHO guidelines (2009) with a few modifications to determine the efficacy of mosquito repellents.

3.1. Search Strategies and Inclusion Criteria

This review used research articles and studies written and published in various journals over the last five years, from 2016 to 2021. Most articles were researched using Google Scholar, ScienceDirect, and PubMed and were accessed using the researchers' accounts and the De La Salle University Library's online databases. To look for published works done by other researchers relevant to the scope, the search terms used were 'mosquito repellent,' 'DEET,' 'secondary metabolites,' 'terpenes,' 'chemical constituents,' and 'repellent activity.'

3.2. Screening Process

With various available publications about the repellent activities of DEET and plant EOs with terpenes, the researchers screened the date of publication and article types, not considering those published earlier than 2016 or were in the form of a review article. The titles and abstracts were then screened; articles that focused on larvicidal activity or did not test against mosquitoes were eliminated. Lastly, the full-text articles of those deemed relevant to the review were checked for eligibility; those that did not provide sufficient information about the active compounds DEET or terpenes and their protection ability against mosquitoes were excluded.

3.3. Data Analysis Strategy

With the researched related works, the researchers presented the properties of the active compounds of chemical-based and plant-based repellents. Essential data and results from the publications, such as the plant species, plant parts used, and the EO's active constituents, DEET or EO concentration in the formulated repellent, repellency rate, protection time, and mosquito species repelled by each of the formulations, were organized and summarized into a table, ordered by the chemical-based DEET, then the plant-based EOs. Analysis and evaluations on the efficacy of different repellent formulations based on protection time were then made to compare the potential of chemical-based and plant-based mosquito repellents.

3. RESULTS AND DISCUSSION

3.1. Active Compounds

Table 1. *N, N-diethyl-3-methyl-benzamide Tested on Aedes aegypti and Anopheles stephensi*

DEET Concentration in Formulated Repellent	Repellency Rate	Repellency Time	Insect Repelled	Reference
25%	100%	6.10 hours	*Anopheles stepehnsi*	Mohammadi et al. (2019)
20%	100%	6 hours	*Aedes aegypti*	Manh & Tuyet (2020)
20%	100%	4 hours	*Aedes aegypti*	Misni et al. (2016)
15%	100%	4 hours		
10%	100%	2 hours		
5%	100%	2 hours		

Table 2. *Plant Essential Oils Tested on Aedes aegypti and Anopheles stephensi*

Plant – part EO was obtained	Active Constituents in EO (GC-MS)	EO Concentration in Formulated Repellent	Repellency Rate	Repellency Time	Insect Repelled	Reference
Peppermint (*Mentha piperita*) – aerial parts	d-limonene (19.72%), thymol (19.02%), carvacrol (12.37%)	50% 50% (Nanoemulsified)	100% 100%	2.89 hours 4.17 hours	*Anopheles stephensi*	Mohammadi et al. (2019)
Eucalyptus (*Eucalyptus globulus*) – leaves	1,8-cineole (59.45%), terpinene (10.91%)	50% 50% (Nanoemulsified)	100% 100%	0.96 hours 5.51 hours	*Anopheles stephensi*	Mohammadi et al. (2019)
Wild mint (*Mentha arvensis*) – fresh plant leaves	menthol (66.04%), menthyl acetate (22.19%), menthone (2.51%), limonene (2.04%)	25% 50% 100%	100% 100% 100%	0.75 hours 1.5 hours 2.75 hours	*Aedes aegypti*	Manh & Tuyet (2020)
Chaste tree (*Vitex trifolia*) – fresh leaf samples	cis-ocimene (44.57%), α -thujene (25.63%), cyclopentene,3-isopropenyl-5,5-dimethyl (18.19%), α-pinene (6.38%)	4% 5% 6%	99.74% 100% 100%	3 hours 3 hours 3 hours	*Aedes aegypti*	Arpiwi et al. (2020)
Lime (*Citrus aurantifolia*) – leaves	limonene, β-pinene - Al-Aamri et al. (2018) [a]	20% 20% (Microencapsulated) 15% (Microencapsulated)	92.76% 100% 100%	1 hour 2 hours 2 hours	*Aedes aegypti*	Misni et al. (2016)
Pomelo (*Citrus grandis*) – fruit peel	limonene, β-pinene, 3-carene - Sajid et al. (2016) [b]	20% 20% (Microencapsulated) 15% (Microencapsulated)	94.67% 100% 100%	1 hour 2 hours 2 hours	*Aedes aegypti*	Misni et al. (2016)
Galangal (*Alpinia galanga*) – rhizome	carotol, eucalyptol - Singh et al. (2020) [c]	20% 20% (Microencapsulated) 15% (Microencapsulated)	96.89% 100% 100%	1 hour 2 hours 2 hours	*Aedes aegypti*	Misni et al. (2016)

ABC other studies that identified the active constituents present in the same EOs were used because the researchers who tested on these EO-based repellents did not perform GC-MS.

The researchers of the present study were able to compile the data from previous studies, as summarized in Tables 1 and 2, because these studies used the same bioassay method or study design wherein the formulated repellents were directly applied to the skin of the forearm of human subjects. The studies provided information about the repellency rate, repellency time, and species repelled by the formulated repellents. Moreover, the DEET or EO concentrations listed in the tables refer to the percentage by volume composition of either DEET or a plant EO in each of the repellents formulated by the researchers.

Table 1 shows the interrelation of the repellency rate and repellency time of a formulated repellent with a particular DEET concentration tested on either Ae. aegypti or An. stephensi. Meanwhile, Table 2 shows the EOs obtained from certain parts of plants whose repellent formulations were tested on either Ae. aegypti or An. stephensi.

As can be seen in Table 1, DEET-based repellents provide long protection times, depending on the DEET concentration, against Ae. aegypti and An. stephensi, thus being widely used in conventional repellents. In contrast, Table 2 shows that all the active constituents in plant EOs identified by the researchers contained an abundance of terpenes as the major compounds, which previous studies explain to provide the potential of plant-based repellents against different mosquito species.

Several studies present the comparable potential of DEET-based and plant-based repellents in terms of protection time. The nanoemulsified eucalyptus-based repellent at 50% concentration having a complete protection time (CPT) of 5.51 hours against An. stephensi (Table 2) is shown to be close to the formulated 25% DEET repellent with a CPT of 6.10 hours against the same species (Table 1).

Meanwhile, the 5% and 10% concentrated DEET-based repellents, which present complete protection against Ae. aegypti after 2 hours (Table 1), exhibit the same repellent potential to a 15% or 20% concentration of a microencapsulated repellent based on the EO of either lime, pomelo, or galangal in terms of the time for complete protection (Table 2). There are even some plants that have demonstrated a longer CPT than the previously mentioned DEET-based repellents. As presented in Table 2, these were the 100% wild mint EO-concentrated repellent, which had a CPT of 2.75 hours, and chaste tree EO-based repellents at a concentration of either 5% or 6%, as they both demonstrated complete protection against Ae. aegypti up to 3 hours post-application. Given that these 5% and 6% chaste tree EO-based repellents already exhibit a high repellency rate at a longer time of protection, although formulated at a low concentration, chaste tree-based formulations with higher concentrations of EO may provide a longer CPT and exhibit a greater potential.

Furthermore, Tables 1 and 2 show that as the EO concentration in the formulated repellent is increased, the corresponding time that provided complete protection also increased. Although DEET-based repellents formulated at higher concentrations of the active compound demonstrate a longer protection time, the risks or concerns in human and

environmental safety associated with their concentrations and their use reduce their advantageous potential. In addition, as shown in Table 2, the nanoemulsion and microencapsulation processes for the formulation of plant-based repellents have significantly increased their protection time and potential, similar to DEET, compared to those that were formulated the standard way, with no additives present. The effects of these additives and methods and the concerns that may come with higher concentrations of plant EOs require further study to potentially widen the use of plant-based repellents.
Such comparisons from different articles over similar variables, including DEET or EO concentration, repellency rate, or protection time, show that plant-based repellents that contain an abundance of terpenes as active constituents indeed have potential repellent properties against various mosquitoes that is comparable to that of DEET.

4. CONCLUSIONS

Comparing the various studies that presented the concentration, repellency rate, and protection time of DEET-based and plant-based repellents, it has been found that both have their potential repellent properties. Some of the repellents formulated with plant essential oils that contain terpenes, depending on the concentration, even exhibit longer protection times than DEET. This clearly shows that essential oil from plants can be utilized as an alternative to DEET-based repellents, which are known to have drawbacks, harms, and disadvantages.

Awareness regarding the potential of repellents based on various plant species that contain terpenes must thus be increased, as they can also be preferred and used as an alternative to chemical-based repellents. Moreover, further research is recommended on the repellents toward other mosquito species and insects, the plants containing other secondary metabolites as major compounds, and the repellent formulations that would improve their longevity and potentially widen their application and utilization.

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