Evolution, Current Status and Prospects of Phyto-Repellents against Mosquitoes

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Abstract. Mosquitoes enjoy wide geographical distribution and act as vectors for diverse pathogenic organisms from viruses to protozoans. Mosquito-borne diseases have a long history with some of them like Malaria dominating the scene for centuries. New diseases like Dengue fever, Zika viral disease etc. get added to the list from time to time. Vector control is an effective and widely accepted strategy in the management of mosquito-borne diseases. Mosquito repellents are an important product range extensively used for the management of mosquito-borne diseases. The research and development activities on mosquito repellents of plant origin have been reviewed in this article and classified into three categories like research reports, patents and commercial products, based on their outcomes. The relevance of plant-based mosquito repellents is discussed with reference to current societal and market trends. The review has revealed an increasing trend among researchers towards product development and entry of effective and innovative products into the market. The market analysis reports also confirm competitive advantage for herbal repellents in the coming years.

1. Introduction

Insects represent one of the most diverse and abundant groups of invertebrates well accounted for their impact on human and environment. They are omnipresent from indoor to the hostile habitats and infamous for their pest status. Mosquitoes belong to a high-risk category of indoor pests, with established identity as vectors for the transmission in human and animal diseases. They represent a diverse family of insects called Culicidae, with 3 subfamilies like Toxorhynchitinae, Anophelinae, and Culicinae comprising more than 3400 species [1]. Mosquitoes enjoy worldwide distribution marking their presence in tropical and temperate regions, including Arctic zone. But they are not recorded from Antarctic zone. They have been reported from high altitudes up to 6000m above sea level on the mountains and 1250m below the sea level in the mines and caves [2]. Latitudinal distribution of mosquitoes has recorded differential patterns for various species. Highest species diversity of mosquitoes has been reported from the Southeast Asia and the Neotropics [3], with a gradient in diversity from the temperate to the tropical regions [4].

The mosquitoes are well known for their invasive tendency and expansion into new territories. Among the vector mosquitoes, the species of Aedes are considered highly invasive, enjoying global presence. Among these, Ae. aegypti and Ae. albopictus represent the predominant species well adapted for successful invasion. The close association of these species with human dwellings, the resistance of their eggs against prolonged desiccation and larval habitats in small and temporary water holdings in the vicinity of human habitation have contributed to their success in invasion and transmission of the pathogens [5].

Mosquitoes have attained a notorious status, through the numbers and types of diseases transmitted by them and the extent of disaster they cause to public health. Despite the technological developments in the healthcare sector, mosquito-borne diseases pose serious challenges. The Encephalitis is a group of mosquito-borne diseases that take a serious toll on human health with a widespread occurrence. Culex spp. of mosquitoes are the vectors of encephalitis and various other viral diseases prevalent in different parts of the world [6]. Many viral diseases such as chikungunya,
dengue, and Zika virus disease are getting elevated to major public health issues during the recent past. Species of *Aedes* have been identified as the principal vectors of these pathogens [5].

The number of diseases transmitted by mosquitoes, their global presence [2], the invasive trend [5] and the metabolic and behavioral resistance possessed by them [7] make the mosquito control process quite tough. Repellence as one of the strategies has been in practice for a long time in the management of mosquito-borne diseases [8]. Mosquito repellents comprise a wide range of compounds of natural and synthetic origins [9]. Similar to other pest management products, synthetic compounds dominate the mosquito repellent product range and market share, DEET (N,N-diethyl-m-toluamide) representing the most popular and effective agent [10]. Regardless of its extensive use as a repellent, this compound has also been reported to have environmental and health risks [11]. This has led to a focused attempt towards developing eco-friendly repellents from natural sources and new formulations of this range are on demand in the market.

Considering the intricacies involved in the vector control strategies for the management of mosquito-borne diseases and demand for the herbal repellents, evaluation of the prospects and challenges of herbal mosquito repellents has been attempted in the current review.

2. Mosquito-Borne Human Diseases

Among the mosquitoes, only 10% of the total species have been categorized as vectors of infectious diseases. Even with this minority status, they pose a formidable challenge to the contemporary healthcare system. The most notorious vectors belong to three genera of the mosquitoes namely, *Anopheles*, *Aedes*, and *Culex* [5]. The mosquitoes transmit diverse groups of pathogens including protozoa, nematodes, and viruses infecting mammalian hosts (Table1). The number of diseases transmitted by mosquitoes is quite extensive and beyond the scope of this review. Therefore, the analysis is limited to the most predominant epidemics with reference to the extent of the devastation and geographical distribution.

<table>
<thead>
<tr>
<th>Sl No.</th>
<th>Disease</th>
<th>Pathogen</th>
<th>Vector mosquito (es)</th>
<th>Remarks</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Malaria</td>
<td><em>Plasmodium falciparum</em> <em>P. malariae, P. ovale,</em> and <em>P. vivax</em></td>
<td><em>Anopheles</em> spp. <em>Culex</em> spp</td>
<td><em>P. vivax</em> most widespread</td>
<td>[12]</td>
</tr>
<tr>
<td>2</td>
<td>Filariasis</td>
<td><em>Wuchereria bancrofti</em> <em>Brugia malayi B. timori</em></td>
<td><em>Culex</em> spp., <em>Aedes</em> spp., <em>Mansonia</em> spp. (Asia-Pacific); <em>Anopheles</em> spp. (Americas); <em>Ochlerotatus</em> spp.</td>
<td>Geographic variation exists in vector species.</td>
<td>[13-17]</td>
</tr>
<tr>
<td>3</td>
<td>Dengue</td>
<td>Dengue virus serotypes DEN-1, DEN-2, DEN-3, DEN-4 and DEN-5</td>
<td><em>Aedes aegypti</em> and <em>Ae. albopictus</em></td>
<td><em>Ae. Albopictus</em> is prominent</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>4</td>
<td>Chikungunya</td>
<td>Chikungunya virus (CHIKV)</td>
<td><em>Aedes aegypti</em> <em>Ae. albopictus</em></td>
<td>-</td>
<td>[18]</td>
</tr>
<tr>
<td>5</td>
<td>Yellow fever</td>
<td>Yellow fever virus</td>
<td><em>Aedes</em> spp., <em>Haemagogus</em> spp., <em>Sabethes</em> spp.</td>
<td><em>Ae. aegypti</em> is dominant vector</td>
<td>[1, 18]</td>
</tr>
<tr>
<td>6</td>
<td>Japanese Encephalitis</td>
<td>JE virus</td>
<td><em>Culex</em> spp., <em>Mansonia</em> spp., <em>Aedes curtipes</em>, <em>Anopheles</em> spp.</td>
<td><em>C. tritaeniorhynchus</em> is the principal vector</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>7</td>
<td>Zika</td>
<td>Zika virus</td>
<td><em>Ae. aegypti</em> <em>Ae. albopictus</em></td>
<td>-</td>
<td>[22]</td>
</tr>
</tbody>
</table>

Table 1. Major mosquito-borne diseases, pathogens and vector mosquito(es).
2.1. Malaria

Malaria probably represents the oldest and the most investigated vector-borne disease, transmitted by mosquitoes (Anopheles spp.) and remaining as a challenge despite the development of technologies and implementation of effective management practices for its prevention and control. About 70-80 species of Anopheles are involved in the transmission of malaria [23-25]. The history of scientific studies on mosquito-borne diseases is limited to the last 100 to 125 years [1] with malaria as one of the most focused epidemics analyzed. The disease has its origin in the West and Central Africa and spread to the Mediterranean, Americas, and Asia through human migration and travel [26]. The epidemic status of the disease has been reported from tropical and temperate regions of the world [27-30].

2.2. Filariasis

Filariasis is one of the neglected diseases, deserving more attention from the public health sector. The disease is caused by the nematode worms infecting the human lymphatic system and transmitted by mosquitoes. Three species of nematodes are causing the disease, namely Wuchereria bancrofti, Brugia malayi, Brugia timori. Of these, W. bancrofti accounts for 90% of the infections world over [31]. Interestingly, parasites causing filariasis get transmitted by different species of mosquitoes in different geographical areas, with the involvement of five genera of mosquitoes (Table 1). There are few reports indicating the difference in vector species among rural and urban areas, Anopheles transmitting the parasite in rural areas and joined by Aedes and Culex species as well in the urban areas [2]. The disease has a long history and is prevalent in the tropical countries, with wide -spread occurrence in the mid -African and southeast Asian countries. A recent mapping study on the occurrence and prevalence of lymphatic filariasis has reported heterogeneous distribution and geographically targeted nature of this disease. A total of 89 countries have been identified with the incidence of filariasis and in 72 countries the disease is endemic and 17 countries the infection crossed the levels of endemic status. [13].

2.3. Dengue

Dengue is an arboviral disease caused by four viruses closely related Flaviruses family of the tropical and subtropical parts of the world [32-34] manifested as two epidemic ailments like Dengue fever (DF) and Dengue Hemorrhagic Fever (DHF). The latter is characterized by leakage of plasma, enhanced vascular permeability, shock, and hypovolemia accompanied by fever and the former with fever, headache and nausea [35]. The annual infection of dengue ranges from 50 to 100 million people across the world [36]. Ae. albopictus and Ae. aegypti have been identified as the vectors of dengue fever and found across the whole belt of the tropical and subtropical regions known for dengue incidence [34]. Ae. albopictus has evolved as a more successful vector of dengue fever due to its ability to efficient vertical transmission of the virus than Ae. aegypti [37] despite its oral receptivity to DENV-2. This species is highly invasive and has established its population worldwide. Before 1979, distribution and invasion of Ae. albopictus was limited to the South-east Asia, China, Japan, Madagascar, the Seychelles and Hawaii. Entry of this mosquito vector into the Europe was first reported from Albania during 1979. First report of Ae. albopictus in the United States was during 1985 followed by Brazil and Mexico in 1986 and the spread across the Central and South America by 2003. In the Mediterranean, Ae. aegypti acted as the major transmitting agent of dengue during the 19th and 20th centuries [18]. By the year 2000 and beyond the mosquito has been attained worldwide distribution [38].

2.4. Chikungunya

Chikungunya virus is an Arbovirus affecting mammals and causes Chikungunya fever in human beings [38]. The virus has its origin in Tanzania and reported during 1953 and spread to other African countries and Asia later. [39, 40]. The disease has gained much public attention since its unprecedented outbreak in Indian Ocean Islands and India during 2005-2007, affecting lakhs of people [40]. Ae. aegypti and Ae. albopictus are the principal vectors of this virus and the disease
ranks as an urban epidemic (Table 1) [18]. A new point mutation was identified from Chikungunya virus which confers the virus an increased fitness for infectivity, dissemination, and transmission in *Ae. albopictus* [41]. Chikungunya fever is characterized by sudden onset of fever followed by the appearance of rashes especially on the face, the trunk and the limbs followed by joint pain, the latter last for a long duration of time ranging from weeks to months together leading to chronic joint pain in several patients. The infection manifests in both endemic and epidemic forms and is a major epidemic in urban Asia [18].

2.5. **Yellow fever**

Yellow fever represents a viral hemorrhagic fever caused by Flavivirus. This disease is infectious but non-contagious and gets transmitted between primates and mosquitoes, mosquitoes being the vectors. Major symptoms of the disease include chills, headache, anorexia, malaise, nausea, vomiting and muscular pain in the lower parts of the body. Severe cases result in intoxication and hemorrhages leading to liver and kidney failure and may turn fatal. This disease is endemic in parts of Africa and enjoys the status of an epidemic in South America [18]. Yellow fever has its origin in tropical Africa [42] and later on invaded other parts of the world [43, 44]. The role of *Ae. aegypti* as the vector of this disease was proposed by Carlos in 1881 and confirmed by Reed and group during 1900 [45]. Currently, it is known that the disease can be transmitted by 14 species of *Aedes* and *Ae. aegypti* acts as the major agent of transmission in urban and semi-urban localities [1].

2.6. **Japanese encephalitis**

This is a dreaded disease caused by Japanese encephalitis (JE) virus, of the Flavivirus group. This virus has been considered as the causative agent for the most common encephalitis worldwide and is endemic in Southeast Asia [46]. This virus infects a wide range of vertebrates, mainly birds, and mammals. The first major epidemic of Japanese encephalitis was from Japan in the year 1924 followed by many during later years [47-50]. The disease may be asymptomatic with mild or high fever accompanied by hallucination in severe cases. Almost 50% of the severe cases are known to cause permanent neurological damage after recovery [51] and fatality rate among children has been reported up to 25% [52].

Several species of mosquitoes belonging to *Culex, Mansonia, Aedes* and *Anopheles* have been identified as the transmitting agents of this disease. However, *Culex tritaeniorhynchus* is rated as the principal vector of JE virus (Table 1). The virus exhibits an animal-vector-human cycle and pigs acts as the major reservoir host [42, 53]. In addition, there are few other members of Flavivirus group causing different neurological infections in different parts of the world such as the West Nile Fever, Rift Valley Fever, Eastern Equine Encephalitis, etc., all being transmitted by mosquitoes [18] and are not dealt in detail in this review, as this work intends to focus more on mosquito repellents.

2.7. **Zika**

Zika virus fever is caused by yet another Flavivirus, named after Zika forest in Uganda, from where it has been discovered among macaque monkeys during 1947. The infection is characterized by fever, rashes, and conjunctivitis with associated joint pain. The symptoms persist for few days to weeks and months in some cases. As such the disease is mild and often people will not seek treatment. However, recent observations on the link between microcephaly and the autoimmune disorder, Guillain-Barré syndrome, a neuromuscular degenerative condition has generated much public anguish regarding Zika infection. The incidence of the infection has been reported from the Caribbean and the native African regions. [55]. *Ae. aegypti* and *Ae. albopictus* have been demonstrated as the vectors of this virus and *Culex pipiens* has been reported to be resistant to infection by the virus [22].
3. Mosquito Repellents: History and Current Status

Repellents are substances or formulations which deter arthropods from touching or biting a host or landing on a surface [56, 57]. Generally, repellents create a barrier of vapour in the immediate surroundings of the protected surface [58]. Therefore, volatile compounds or materials containing them find application for this purpose. Four important insect repellents of early years comprised Citronella oil, Dialkyl Phthalates, Indalone, and Rutgers 612 [58]. The history of insect repellent commercial products dates back to 1929 and first patented repellent formulation of synthetic compounds, Indalone® got registered during 1937 [8] and enjoyed wide use during the 1940s and 1950s. Ever since its authentic introduction in the US market during 1956, DEET (N,Ndiethyl-m-toluamide) remained as the most popular active ingredient in synthetic commercial mosquito repellent formulations [10, 59], despite its environmental and human health risks [11, 60]. A synthetic pyrethroid, Permethrin was introduced during 1973 as an alternative to DEET [59] and widely used in the preparation of mosquito repellent nets for the control of Malaria in the United States [61, 62]. Picaridin [2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester] is another compound introduced in Australia, Europe, and the US since 1998 for mosquito control [63] and this compound has been approved by the WHO as well [64]. The DRDO, India has confirmed the insect repellent property of N, n-dialkyl -morpholin- 4 - carboxamide compounds and developed a process for their synthesis [65].

There is an increasing concern among the public on environmental and health risks associated with mosquito repellent products, driving the scientific community towards the development of environmentally sustainable repellents against the mosquitoes. Use of natural products and essential oils as insect repellents has been known widely. Essential oils of plants and mixtures of plant-derived volatile compounds find application in repellent formulations, being used extensively against blood-sucking arthropods [66]. Mosquito repellent property of citronella oil was known before 1940 and is still in use for this purpose, even though its efficacy is inferior when compared to synthetic compounds [58]. Many studies conducted on the extracts and oils of plants such as Artemisia vulgaris, Lantana camara, Vitex negundo, lemon grass and eucalyptus have confirmed to display a repellent activity against mosquitoes [17, 67, 68].

Though the use of plant-derived essential oils as mosquito/insect repellent has a long history, efforts towards developing commercial formulations from them remained as a low-key affair until the late 1990s. The short-term activity of the oils has been identified as a major limiting factor in their success as repellents [69, 70]. Lemon, eucalyptus, and citronella oils have been registered as ingredients for insect repellents under the US Environmental Protection Agency (US EPA). The registration enables the use of these oils in topical application formulations against mosquitoes and is being widely used in mosquito repellents due to their low toxicity, customer acceptance and competency near to that of synthetic chemical repellents [59].

In order to derive a realistic conclusion based on the research and development of plant-derived mosquito repellents and their practical application, the literature on herbal mosquito repellents screened for the preparation of the current article have been categorized as illustrated in Fig. 1 below.
As depicted in Fig. 1, a total of 71 papers were screened for data/information on the application of plant derived mosquito repellents. Many of the articles got eliminated at two different levels due to the paucity of data or methods employed or lack of clarity.

### Relevant Studies from the Phyto-Repellent Activities

A brief summary of the outcomes of the important articles selected for analysis is presented in Tables 2a and 2b. The articles have been categorized into research reports, field trials and patents, in Table 2a and commercial products are listed in Table 2b.
Table 2a. Current status of research on phyto-repellents against mosquitoes.

<table>
<thead>
<tr>
<th>Type of articles</th>
<th>Description</th>
<th>Formulation type/mosquito vector(s)/study type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanillin &amp; essential oils</td>
<td>Ae. Aegypti</td>
<td>[71]</td>
<td></td>
</tr>
<tr>
<td>Neem &amp; coconut oils</td>
<td>Anopheles spp.</td>
<td>[72]</td>
<td></td>
</tr>
<tr>
<td>Nipetalactone from Catnip</td>
<td>Mosquitoes</td>
<td>[8]</td>
<td></td>
</tr>
<tr>
<td>Z limonella</td>
<td>Mosquitoes</td>
<td>[73]</td>
<td></td>
</tr>
<tr>
<td>Carapa guianensis Aubl. (Andiroba) oil</td>
<td>Aedes spp.</td>
<td>[74]</td>
<td></td>
</tr>
<tr>
<td>Catnip oil</td>
<td>Cx pipiens</td>
<td>[75]</td>
<td></td>
</tr>
<tr>
<td>Essential oils of Eucalyptus globulus, Ocimum basilicum Cymbopogon citratus Citrus sinensis, Azadirachta indica ) and Hyptis suaveolens</td>
<td>Laboratory bioassay against A. gambiae</td>
<td>[76]</td>
<td></td>
</tr>
<tr>
<td>Analysis of mosquito repellent treated textile materials</td>
<td>Mosquitoes</td>
<td>[77]</td>
<td></td>
</tr>
<tr>
<td>PMD with insecticide (Deltamethrin) treated bed nets</td>
<td>Field trial</td>
<td>[78]</td>
<td></td>
</tr>
<tr>
<td>Vitex negundo leaf extract</td>
<td>Field trial</td>
<td>[79]</td>
<td></td>
</tr>
<tr>
<td>Citronella leaf &amp; neem powder cake impregnated with citronella oil</td>
<td>Laboratory and small scale field study</td>
<td>[80]</td>
<td></td>
</tr>
<tr>
<td>Handmade paper coated with herbal extracts</td>
<td>Herbal fast card against mosquitoes; field trial</td>
<td>[81]</td>
<td></td>
</tr>
<tr>
<td>Neem, cedar &amp; citronella oil US patent No. US00588560</td>
<td>Test formulation; mosquitoes</td>
<td>[82]</td>
<td></td>
</tr>
<tr>
<td>Essential oils of Tagetes minutum, cedar wood, Chrysanthemum caenararifolium &amp; Cyperus rotundus</td>
<td>Repellent incense stick; field trials; mosquitoes</td>
<td>[83]</td>
<td></td>
</tr>
<tr>
<td>Mosaway: Plant extracts and essential oils; Indian Patent No. Patent No. 656/DEL/97 by CIMAP by CIMAP, India</td>
<td>Vanishing cream;</td>
<td>[85]</td>
<td></td>
</tr>
<tr>
<td>Mospray: Plant extracts and essential oils; Indian Patent No.186120 by CIMAP, India</td>
<td>Spray</td>
<td>[85]</td>
<td></td>
</tr>
<tr>
<td>MosEx: Patent No. 656/DEL/97 by CIMAP, India</td>
<td>Body lotion</td>
<td>[85]</td>
<td></td>
</tr>
<tr>
<td>MOSNOTE: Indian patent appln No. 226NF/2005 by CIMAP, India</td>
<td>Liquid vaporizer</td>
<td>[85]</td>
<td></td>
</tr>
<tr>
<td>MosRep: Incense stick, Chinese patent No. ZL00801425.6 by CIMAP, India</td>
<td>Mosquitoes</td>
<td>[85]</td>
<td></td>
</tr>
<tr>
<td>144 patents on plant derived mosquito repellents between 1991- 2010.</td>
<td>Mosquitoes</td>
<td>[86]</td>
<td></td>
</tr>
<tr>
<td>Lemongrass oil, rose geranium oil, lemon eucalyptus oil, and Litsea cubeba oil:</td>
<td>Body spray or impregnation to fabric or other wearable devices, repellent against mosquitoes</td>
<td>[87]</td>
<td></td>
</tr>
<tr>
<td>2-phenylacetamide from plants: Indian patent 268615</td>
<td>Test formulation; mosquitoes</td>
<td>[88]</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2b. Commercial mosquito repellent products of plant origin.

<table>
<thead>
<tr>
<th>Type of articles</th>
<th>Description</th>
<th>Formulation type/mosquito vector(s)/study type</th>
<th>Percentage or concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quwenling: eucalyptus oil &amp; p-methanodiol; Chinese product</td>
<td>Mosquitoes</td>
<td>50%</td>
<td>[89]</td>
<td></td>
</tr>
<tr>
<td>Buzz Away®, Green Ban®: Essential oil based</td>
<td>Mosquitoes</td>
<td>Not available</td>
<td>[90]</td>
<td></td>
</tr>
<tr>
<td>Repel, lemon eucalyptus oil, by Spectrum Brands</td>
<td>Mosquitoes</td>
<td>40%</td>
<td>[91]</td>
<td></td>
</tr>
<tr>
<td>Herbal Armor, All Terrain, Sunapee, NH, USA; citronella oil</td>
<td>Mosquitoes</td>
<td>5-15%</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>Natrapel, by Tender Corporation, Littleton, USA, citronella oil</td>
<td>Mosquitoes</td>
<td>5-15%</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>Green Ban by Green Home, San Francisco, California, USA, citronella oil</td>
<td>Mosquitoes</td>
<td>5-15%</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>Cutter natural insect Repellent: Geraniol (5%) &amp; Soybean oil;</td>
<td>Spray; Mosquitoes</td>
<td>2%</td>
<td>[92]</td>
<td></td>
</tr>
<tr>
<td>Cutter lemon eucalyptus insect repellent: Oil of lemon eucalyptus; Spectrum Division of United Industries Corporation</td>
<td>Spray; Mosquitoes</td>
<td>30%</td>
<td>[92]</td>
<td></td>
</tr>
<tr>
<td>EcoSmart organic insect Repellent: EcoSMART Technologies Inc.</td>
<td>Spray; Mosquitoes</td>
<td>Geraniol -1.0%, Rosemary oil - 0.5%, Cinnamon oil - 0.5% &amp; Lemongrass oil - 0.5%</td>
<td>[92]</td>
<td></td>
</tr>
<tr>
<td>Avon Skin So Soft Bug Guard: Oil of citronella; Avon Products, Inc</td>
<td>Spray; Mosquitoes</td>
<td>10%</td>
<td>[92]</td>
<td></td>
</tr>
<tr>
<td>Mosquito skin patch: Thiamin B1; AgraCo Technologies International, LLC</td>
<td>Skin patch; Mosquitoes</td>
<td>300mg</td>
<td>[92]</td>
<td></td>
</tr>
</tbody>
</table>

### 4.1. Research reports

Repellency of Nepetalactone isolated from Catnip has been reported as comparable to that of DEET [8]. Study on the mosquito repellent activities of the essential oils of three different plants *Zanthoxylum limonella* (fruits), *Citrus aurantifolia* (leaf), and petroleum ether extract of *Z. limonella* (fruits), in both mustard and coconut oil base have confirmed superior mosquito repellent activity than *Z. limonella* over the others with activity extending 294-304 minutes [73]. Comparative evaluation of the repellent activity of Andiroba (*Carapa guianensis*) oil with DEET 50% as a topical application on human volunteers against *Aedes* sp has confirmed the effective repellent status of the oil, but not at par with DEET 50% [74]. Schultz et al. [75] have demonstrated the
repellency of Catnip oil on *Culex pipiens* at par with that of DEET, except the residual activity period which was found more with the latter. Formulations of essential oils of *Eucalyptus globulus, Ocimum basilicum, Cymbopogon citratus, Citrus sinensis, Azadirachta indica* and *Hyptis suaveolens* prepared individually with ethanol, water, and polyethylene glycol have yielded 68-95% repellent activity against *A. gambiae* lasting for 2 hours in a laboratory comparison with commercial products like Odomus ® [76]. Standardization and optimization of the evaluation method are critical before patenting/product development. Application of mosquito repellents on textile is a novel approach for mosquito control. A recent review on this aspect, [77] has analyzed textile material selection, methods of incorporation of repellents to the fabric and methods for the efficacy evaluation of treated textile materials. The review has reported the suitability of cotton, polyester and blended fabrics for the purpose and highlighted the need for optimization of techniques for impregnation of the mosquito repellent(s) to different fabrics, in order to achieve better efficacy. A topical application formulation of neem oil (2%) with coconut oil has been reported to provide 12 hr protection against biting from *Anopheles* mosquitoes [72].

4.2. Field trials

The positive impact of the synergistic action of PMD with insecticide (deltamethrin) treated bed nets in preventing malaria has been reported from Bolivian Amazon by Hill et al. [78]. Field study reports from Bolivia and Tanzania using topical application of 20% PMD have reported successful repellent activity against mosquitoes up to 4-6 hrs. [93]. Citronella leaf cake from waste leaves after oil extraction mixed with neem powder impregnated with 10% citronella oil has been reported as an effective repellent against mosquitoes under laboratory and semi-field trials [80]. Development and efficacy evaluation of herbal fast card made of handmade paper coated with extracts of *V. negundo, A. indica, Ocimum sanctum, Curcuma longa, Cinmomum camphor, and Cymbopogon citratus* [81] has confirmed long lasting repellent activity of the fast card on burning, against mosquitoes. Mosquito repellent efficacy of *Vitex negundo* leaf extract impregnated terryt fabric wearing devices (armbands, anklets, collars, etc.) against mosquitoes in the field up to 6-8 hrs has been reported by Karunamoorthi et al. [79]. Field trial of polyherbal extract/essential oils formulations in the form of gel and spray formulations in Sri Lanka has confirmed 100% mosquito repellency in both laboratory and field trials [94].

4.3. Patents

An insect repellent composition containing essential oils of Neem, Cedarwood and Citronella along with an antioxidant and indications for its different types of the formulation was invented and reported by Blum et al. [82]. An herbal mosquito repellent formulation comprising essential oils of *Tagetes minuta*, cedar, *Chrysanthemum cinerariaefolium* (Pyrethrum powder) and *Cyperus rotundus* and its use as incense stick was patented by Kumar et al. [83]. Iyer et al. [84] have claimed a novel insecticidal and mosquito repellent compound from the oil of the plant Blumea lacera and the methods for preparation of liquid vapor and mat formulations from the oil. CIMAP, India has patented five novel formulations of herbal mosquito repellents [85] (Table 2). In an extensive survey and analysis of patents granted on herbal based mosquito repellents across the world by Pohlit et al. [86] have reported more than 50 plants as the natural sources of repellent compositions. A repellent composition of natural oils of lemongrass oil, rose geranium oil, lemon eucalyptus oil, and *Litsea cubeba* oil in the form of body spray has been reported and patented by Salomon et al. [87]. In still another application DRDO has patented 2-phenylacetamide compounds from plants for the preparation of insect repellents in the form of creams, sprays or other formulations [88].

4.4. Commercial products

The competitive advantage of a Chinese formulation called Quwenling from Eucalyptus oil containing PMD (*p*-menthane-3,8-diol) over DEET in commercial market has been reported by Triigg [89]. However, comparative evaluation of the repellence of two natural oil-based commercial formulations (Buzz Away®, Green Ban®), two proprietary products (Skin-So-Soft lotion and bath oil), and 8 commercial DEET preparations using laboratory olfactometer by Chou et al. [90]
reported a higher efficiency of DEET formulation over the others. Repel, another brand of mosquito repellent derived from the oil of the lemon eucalyptus oil. Comparative evaluation of lemon eucalyptus spray formulation with 10% DEET has confirmed efficacy of the oil comparable to that of DEET and provided protection up to 7 hrs against aggressive species of mosquitoes and more than 12 hours against less aggressive species according to a study conducted by Stjernberg and Berglund [91].

A recent comparative analysis of four essential oil-based commercial body spray formulations and a skin patch made of vitamin B1, with 3 different formulations of DEET [92] has rated the formulations containing DEET or PMD with prolonged active period of repellent activity and the skin patch containing Vit B1 with no repellent activity against *Aedes* spp. (Table 2). Citronella based natural mosquito repellents in the US market include Herbal Armor (All Terrain, Sunapee, NH), Natrapel (Tender Corporation, Littleton, NH), and Green Ban (Green Home, San Francisco, Calif). But the duration of protection of all the 3 products ranged from 20-30 minutes only [59]. Schreck and Leonhardt [95], have concluded that nearly 50% of non-US-produced insect repellents contained natural oils and DEET (*N*, *N*-diethyl-*m*-toluamide), as the active ingredients, based on their evaluation of Chinese mosquito repellent products.

### 4.5. Phyto-repellent molecules and their activities

The set of phytochemical molecules identified with definite repellent activity towards mosquitoes is quite large. Fig. 2 provides the chemical structure of some of the important phytochemical repellent molecules [96]. Important phytochemical molecules with confirmed activity and their source plants are listed in Table 3. The volatile compounds are suitable for special repellent formulations and the contact repellents can find use in spray or skin application formulations. The mechanism of action of repellent molecules varies widely and is explored with respect to very few phytochemicals.

The repellent molecules interact with olfactory and gustatory receptors in the mosquitoes. The mechanisms of repellent activity vary among insects, depending on the type of repellent molecules. Picaridin (piperidine carboxylate) and citronellal stimulates specific Gustatory receptor Neurons of the antenna in the mosquitoes eliciting an aversive behavior towards the compound in *Ae. aegypti* [97]. Activation of TRPA1 gene has been reported as eliciting aversive response [98]. Attenuation or masking of the perception to host odorants by the antennal sensors is an alternative mechanism reported for the repellent activity of picaridin in different vector mosquitoes like *Aedes* spp., *C. quinquefasciatus*, and *A. minimus* [99,100].

Table 3. Phytorepellent molecules and their source plants.

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Compounds &amp; Structure</th>
<th>Type of activity</th>
<th>Major source plants</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Picaridin (piperidine carboxylate)</td>
<td>Contact repellent</td>
<td>Pepper</td>
<td>[63]</td>
</tr>
<tr>
<td>2</td>
<td>Citronellal</td>
<td>Spatial repellent</td>
<td>Citronella, Lemon eucalyptus</td>
<td>[93]</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Name</td>
<td>Category</td>
<td>Plant Source</td>
<td>Reference</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------</td>
<td>---------------------------</td>
<td>-----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>3</td>
<td>PMD [p-methane 3-diol]</td>
<td>Spatial repellent</td>
<td>Lemon eucalyptus</td>
<td>[78]</td>
</tr>
<tr>
<td>4</td>
<td>Vanillin</td>
<td>Stability enhancer</td>
<td>Vanilla</td>
<td>[71]</td>
</tr>
<tr>
<td>5</td>
<td>Neptalactone</td>
<td></td>
<td>Catnip</td>
<td>[8]</td>
</tr>
<tr>
<td>6</td>
<td>Cyperene</td>
<td>Spatial repellent</td>
<td>Nut sedge (Cyperus rotundus)</td>
<td>[83]</td>
</tr>
<tr>
<td>7</td>
<td>Geraniol</td>
<td>Spatial repellent</td>
<td>Lemongrass</td>
<td>[93]</td>
</tr>
<tr>
<td>8</td>
<td>Eugenol</td>
<td>Spatial repellent</td>
<td>Clove, Eucalyptus</td>
<td>[93]</td>
</tr>
<tr>
<td>9</td>
<td>2-phenyl acetamide</td>
<td>Spatial repellent</td>
<td></td>
<td>[88]</td>
</tr>
<tr>
<td>10</td>
<td>Citronellol</td>
<td>Spatial repellent</td>
<td></td>
<td>[93]</td>
</tr>
</tbody>
</table>
5. Challenges, Prospects and Markets of Herbal Repellents

The information and data provided in the literature are indicative of the growing popularity and relative efficacy of the herbal repellents against mosquitoes and the current extent of practical application of such products. Now it is obvious that this field of research has picked up pace as more and more translational research outcomes have been recorded across the countries during the recent past (Table 2). Meanwhile, the competitive efficacy of the herbal products, especially in terms of residual activity is apparent in many of the comparative evaluation reports [69, 70]. Cost-effectiveness is a second impediment in the establishment of herbal mosquito repellents for the routine field applications. The higher cost and lower stability of the active components of herbal repellents account for their lower ranking in comparison with synthetic chemical repellent compounds, in terms of consumer acceptance and success in the market.

Similar to any other, repellents, development of resistance by the mosquitoes is the third deterrent that intervenes with the success of herbal mosquito repellents. The resistance mechanisms in mosquitoes towards repellents are wide-ranging comprising behavioural, physiological, and molecular dimensions [7]. Radical behavioural change in host searching pattern, with a shift from nocturnal to crepuscular biting habit of Anopheles mosquitoes over the time has been reported, which in turn, propounds challenge in malaria vector control program using long lasting insecticidal nets, being employed at community levels [101, 102]. The best understood molecular mechanism of resistance to repellents/insecticides is the modification of the target molecules of the repellents/insecticides, so as to avoid their action. Such changes have been observed in common insecticide target molecules like acetylcholinesterase (AChE), the voltage- dependent sodium channel (CNaVdp), and the receptor of γ -aminobutyric acid [103-105]. Physiological resistance strategy involves the production of three major types of enzymes for the detoxification of the exotic compounds, including the insecticides. The major enzymes involved in this activity include esterases, cytochrome P450 monooxygenases, and glutathione-S-transferases [94]. Cellular mechanism of the pyrethroid resistance of A. funestus observed in Mozambique has revealed overexpression of P450 gene and complementary role of glutathione-S-transferases [7].

The major factors contributing towards the prospects of herbal repellents lie in their heterogeneity and complexity, which imparts formidable challenge to the resistance mechanisms of the mosquitoes. Unlike the synthetic chemical repellent compounds, herbal extract, oils or their fractions contain multiple ingredients [106, 107] and hence less susceptible for resistance development by the mosquitoes. Lower residual toxicity and human-friendly nature of the essential oils and natural repellents enjoy wide popularity and acceptance among the public [101]. These factors may exert a positive impact in driving the success of these products in the market. An overall rise in demand for mosquito repellents is quite obvious in the global market due to an increase in the mosquito-borne diseases coupled with population explosion of mosquitoes under the influence of global warming and other climate change factors [108, 109].

Mosquito repellents represent one of the crucial healthcare product segments enjoying global presence. Asia-Pacific region accounts for the largest share in the world market of mosquito repellents due to the higher demand in China and India [108]. Indian insect repellent sales touched INR 4400 Crore per annum in the retail market according to a report by the Euromonitor and coils account for almost 50% of the total sales [110]. A steady growth in the mosquito repellent market is affirmed in India and is related to the increasing health consciousness and evolved literacy rate among the public [111]. Mosquito repellents have been reported as the majority stake of the insect repellent market in the United States [8], indicating their dominance in the American market as well. Sandler Research, Pune, an India-based market analyst in its market report (2015), has predicted 7.44% growth in mosquito repellent market at global level up to 2019 and forecasted organic products as the driving force [109]. A surge in demand for mosquito repellents has been witnessed in the America and Africa during recent times owing to the Zika virus threat [108].

Market penetration of herbal and organic mosquito repellents in varied formulations like sprays, creams and oils are at higher levels in the developed countries such as Europe and North America. Meanwhile, a steady increase in the demand for such premium products is obvious in the
developing markets as well [108]. Complementing the demand, there is a surge in new players in the market with innovative and user-friendly product range in the mosquito repellent segment [87, 92, 112]. Value addition to the product range reinforced with increased awareness, changing lifestyle, publicity campaigns from government and private organizations have set the track for a consistent growth of eco-friendly mosquito repellents among the developing countries [108].

6. Future Direction for Phyto-Repellents in the Fight against Mosquitoes

The foregoing analysis of mosquito-borne diseases, mosquito vectors transmitting them, research and development activities on mosquito repellents, novel product range and the market trends for the products have implied a remarkable growth in the development, demand, and usage of mosquito repellents, especially those of herbal/organic origin. Enhancement of the efficacy and stability of these products enable them to be treated at par with chemical repellents. Amines and pyridines have been identified as a major source of insect repellents in plants [113]. However, the synergistic activities of different metabolites present in the essential oils have been predicted to exert higher bioactivity compared to that of isolated components [106, 107]. Use of additives in the formulations is one of the strategies adopted for efficacy improvement and extension of the activity period of herbal repellents. Several additives like liquid paraffin [114, 115], salicylic acid [56], mustard and coconut oils [116] have been evaluated for enhancing the repellency of essential oils against mosquitoes. Vanillin represents a widely used additive for the purpose [57,115], as its positive role in the enhancement of the protection time has been confirmed against A. aegypti [71]. Sustained release of the active components is a more recent approach being explored for value addition to herbal repellent formulations in terms of activity period and effectiveness. A method for the preparation of chitosan encapsulated citronella oil microcapsules for the controlled release of the oil was optimized by Hsieh et al. [117].

A wide range of other strategies for the improvement of herbal products in terms of effectiveness, stability, and mode of application are being explored extensively. Nanoemulsions [118, 119], novel and improved formulations [57, 120, 121], formulations for spatial applications [122-126] and excito repellents are few to name. Nerio et al. [127] have endorsed the potency of plant essential oils as an effective resource for developing environment-friendly mosquito repellent formulations and discussed the synergistic activity of other natural compounds like vanillin for enhancing the mean time of effectiveness of the formulations. The authors further analyzed repellency evaluation studies of various essential oils by different authors and discerned oils of Cymbopogon and Eucalyptus as the most potential and widely used natural repellents.

7. Conclusion

Mosquito-borne diseases are a global challenge in the public health sector and demand targeted management efforts, with mosquito control representing the most crucial strategy. Mosquito repellents make a major share of mosquito control products across the world. Mosquito repellents of plant origin are gaining a foothold in the market owing to the increasing environmental concern among the consumers. Innovative products and formulations are entering the market during the recent times. Analysis of the market trends strongly predicts a definite growth and expansion for mosquito repellents and a paradigm shift from the conventional chemical-based formulations to herbal and organic products in the near future across the world.
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