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Commercial Mosquito Repellents and Their Safety Concerns

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Abstract

Mosquitoes are serious vectors of diseases threading millions of humans and animals worldwide, as malaria, filariasis, and important arboviruses like dengue, yellow fever, chikungunya, West Nile virus, and Zika viruses. The swift spread of arboviruses, parasites, and bacteria in conjunction with the development of resistance in the pathogens, parasites, and vectors represents a great challenge in modern parasitology and tropical medicine. Unfortunately, synthetic insecticides had led to some serious health and risk concerns. There are no vaccines or other specific treatments for arboviruses transmitted by mosquitoes. Accordingly, avoidance of mosquito bites remains the first line of defense. Insect repellents usually work by providing a vapor barrier deterring mosquitoes from coming into contact with the skin surface, and this chapter focused on assets and liabilities, mechanism of action, improving efficacy, safety, and future perspective of synthetic and natural repellents that could potentially prevent mosquito-host interactions, thereby playing an important role in reducing mosquito-borne diseases when used correctly and consistently.

Keywords: repellent plants, synthetic repellents, treated clothes, nanoparticles, microencapsulation

1. Introduction

Parasites since antiquity [1] are a serious threat for millions of humans and animals worldwide which bring about chronic debilitating, periodically disabling disease and are responsible for the overwhelming financial loss [2–6]. Mosquitoes (*Diptera: Culicidae*) [7, 8] are among them as they can act as vectors for serious parasites and pathogens, including malaria, filariasis, and important arboviruses, such as dengue, yellow fever, chikungunya, West Nile virus, and Zika viruses [9, 10]. Mosquito control and personal protection from mosquito bites are the most meaningful measures for controlling several life-threatening diseases transmitted exclusively by bites from bloodsucking mosquitoes. Repellents evolved, dates back to antiquity; the Pharaoh Sneferu, reigned from around 2613–2589 BCE and the founder of the fourth dynasty of Egypt, and Cleopatra VII, the last pharaoh of ancient Egypt, used bed nets as protection against mosquitoes; the ancient Egyptians used essential oils (EOs) for repelling insects, medicinal benefits, beauty

care, and spiritual enhancement and in literally all aspects of their daily life [1]. Insect-repellent plants have been applied traditionally for thousands of years through different civilizations [11]. Such plants were used in various forms such as hanged bruised plants in houses, crude fumigants where plants were burnt to drive away mosquitoes, and oil formulations applied to the skin or clothes [12]. Smoke is undoubtedly the most extensively exploited means of repelling mosquitoes, typically by burning plants in rural tropics and by utilizing spiral-shaped incenses like Katori Senk—an archetypal icon of the humid Japanese summers [13].

Mosquitoes have been considered as a major obstacle to the tourism industry and socioeconomic development of developing countries particularly in the tropical and endemic regions [14]. Mosquito problems are ancient as old as the pyramids, and the presence of malaria in Egypt from circa 800 BCE onward has been confirmed using DNA-based methods, and antigens produced by *Plasmodium falciparum* leading to tertian fever in mummies from all periods were detected, and all mummies were suffering from malaria at the time of their death [1]. Herodotus noted down that the builders of the Egyptian pyramids (circa 2700–1700 BCE) were given large amounts of garlic almost certainly to protect them against malaria [1]. Despite recent considerable efforts to control vector-borne diseases, malaria alone produces 250 million cases per year and 800,000 deaths including 85% of children under 5 years [15]. Global warming has moved the mosquitoes on the way to some temperate and higher altitudes, affecting people who are vulnerable to such diseases [16]. Recently, malaria is a great problem in Africa, but it was well controlled in Egypt [1]. Ahead of the development and commercial success of synthetic insecticides in the mid-1930–1950s, botanical insecticides were the leading weapons for insect control. Synthetic insecticides are distinguished by their efficacy, speed of action, ease of use, and low cost. Therefore, they drove many natural control methods as botanicals, predators, and parasitoids to shadows [8, 17, 18]. Insecticidal treatment of house walls, in particular, could provide a very helpful reduction of mosquito incidence, but such measures need financial and organizational demand, but poor rural areas in endemic regions do not have sufficient resources for such costly protective measures. Because of health and environmental concerns [8, 17], there is an urgent need to identify new nonhazardous vector management strategies that replace harmful chemical insecticides and repellents. There are no vaccines or other specific treatments for arboviruses transmitted by mosquitoes; therefore, avoidance of mosquito bites remains the first line of defense [9, 18]. Hence, the use of the mosquito repellents (MRs) on exposed skin area is highly recommended.

Insect repellents usually work by providing a vapor barrier deterring mosquitoes from meeting the skin surface. Insect repellents had been used for thousands of years against biting arthropods. Several species of primates were observed anointing their pelage via rubbing millipedes and plants as *Citrus* spp., *Piper marginatum*, and *Clematis dioica*. Wedge-capped capuchins (*Cebus olivaceus*) were observed rubbing the millipede *Orthoporus dorsovittatus* onto their coat during the period of maximum mosquito activity [19]. Such millipede contains benzoquinones and insect-repellent chemicals, and it was hypothesized that the anointing behavior was intended to deter biting insects. Laboratory studies revealed a significant repellent effect of benzoquinones against *Aedes (Stegomyia) aegypti* (the yellow fever mosquito) and *Amblyomma americanum* (the lone star tick). Such anointing behavior to deter blood-feeding arthropods is also common among birds, and it could be genetically expressed as an “extended phenotype” as it has an obvious adaptive advantage. Evidence for this lies in the fact that benzoquinones applied to filter paper elicited anointing activity among captive-born capuchins [12]. The World Health Organization (WHO) also recommends repellents for protection against malaria as the resistance of *Plasmodium falciparum* to anti-malarial drugs

such as chloroquine is increased. Most of the commercial MRs are prepared using non-biodegradable, synthetic chemicals like *N,N*-diethyl-3-methylbenzamide (DEET), dimethylphthalate (DMP), and allethrin which may lead to the environment and, hence, the unacceptable health risks in the case of their higher exposure. With an increasing concern for public safety, a renewed interest in the use of natural products of plant origin is desired because natural products are effective, environmentally friendly, biodegradable, inexpensive, and readily available [7, 8, 13, 17, 20]. Repellent application is a reliable mean of personal protection against annoyance and pathogenic infections not only for local people but also for travelers in disease risk areas, particularly in tropical countries; therefore, this chapter focused on assets and liabilities, safety, and future perspective of synthetic and natural MRs that could potentially prevent mosquito-host interactions, thereby playing an important role in reducing mosquito-borne diseases when used correctly and consistently.

2. Synthetic repellents

The history of synthetic repellents had been reviewed [12]; before World War II, MRs were primarily plant-based with the oil of citronella being the most widely used compound and the standard against which others were evaluated. At that time, the emergence of synthetic chemical repellents starts. There were only three principal repellents: dimethylphthalate discovered in 1929, Indalone® (butyl-3,3-dihydro-2,2-dimethyl-4-oxo-2*H*-pyran-6-carboxylate) patented in 1937, and Rutgers 612 (ethyl hexanediol), which became available in 1939. Later on and for military use, 6-2-2 of M-250 (a mixture of six parts DMP and two parts each Indalone® and Rutgers 612) was used [13]. The event of World War II was the primary switch on in the development of new repellent technologies because the Pacific and North African theaters posed significant disease threats to allied military personnel. Over 6000 chemicals had been tested from 1942 to 1947 in a variety of research institutions led to the identification of multiple successful repellent chemistries. Such great aim established several independent research projects that inevitably identified one of the most effective and widely used insect repellents to date, DEET. From then on, several compounds have been synthesized relying on previous research, which identified amide and imide compounds as highly successful contact repellents. Among these are picaridin, a piperidine carboxylate ester, and IR3535, which are currently considered DEET competitors in some repellency bioassays [21]. The chemical structures of some synthetic repellents are shown in Figure 1.

2.1 DEET

DEET (*N,N*-diethyl-3-methylbenzamide) is the standard and most effective broad-spectrum insect-repellent component with a long-lasting effect on mosquitoes, ticks, as well as biting flies, chiggers, and fleas. DEET was discovered as a mosquito repellent by the US Department of Agriculture and patented by the US Army in 1946. It was allowed for public use in 1957, and since then it has been a standard repellent for several insects and arthropods [14]. DEET is the most studied insect repellent and mainly used as a positive control to compare the efficacy of many repellent substances. DEET has a dose-dependent response: the higher the concentration, the longer the protection. DEET, 20–25%, is the conventional concentration used in commercial products. The shorter protection time depended on the mixture as well [14]. In fact, DEET plays a limited role on

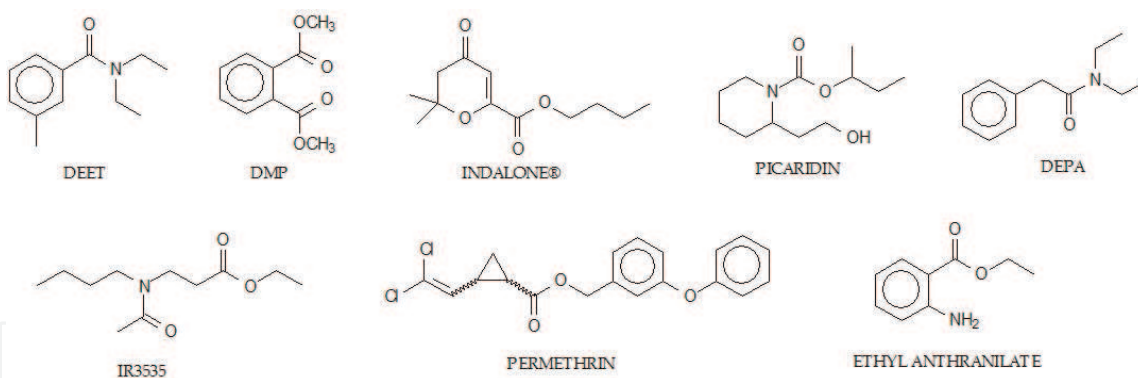


Figure 1.
Chemical structures of some synthetic repellents.

disease control in endemic regions because of its high cost, unpleasant odor, and inconvenience of the continuous application on the exposed skin at high concentrations [22, 23].

2.2 Permethrin

Permethrin is a pyrethroid insecticide derived from the plant *Chrysanthemum cinerariifolium*. It was registered in the US in 1979 as both repellent and insecticide. Recently, it is the most common insecticide available for use on fabrics such as clothing, bed nets, etc. for its exclusive role as a contact insecticide via neural toxicity and equally as an insect repellent [7, 8, 13, 17]. The protection offered against a broad range of bloodsucking arthropods with negligible safety concerns ranked permethrin-treated clothing an important arthropod protection technique especially when used in combination with other protection strategies as applying topical repellents [13].

2.3 Picaridin

Picaridin (1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester) is a colorless, nearly odorless piperidine analog that was developed by Bayer in the 1980s through molecular modeling [12]. It is also known as KBR 3023, icaridin, hydroxyethyl isobutyl piperidine carboxylate, and *sec*-butyl-2-(2-hydroxyethyl)-piperidine-1-carboxylate. Its trade names include Bayrepel and Saltidin, among others. Picaridin was first marketed in Europe in the 1990s and later in the US in 2005 [24, 25]. The efficacy of picaridin is as good as DEET, and notably, 20% picaridin spray was found to protect against three main mosquito vectors, *Aedes*, *Anopheles*, and *Culex* for about 5 h with better efficacy than that of DEET. Therefore, repeated application is required every after 4–6 h [13]. In Australia, a formulation containing 19.2% picaridin provided similar protection as 20% DEET against *Verrallina lineata* [26]. The same formulation provided >95% protection against *Culex annulirostris* for 5 h but only 1-hour protection against *Anopheles* spp. [26]. Picaridin at concentrations of 2–13% *v/v* in 90% ethanol showed better protection against anophelines in Africa than comparable formulations containing DEET [27]. Field studies against mosquitoes in two locations in Australia indicated that a 9.3% formulation only provided 2-hour protection against *V. lineata* [26, 28]. It had been concluded that studies showed little significant difference between DEET and picaridin when applied at the same dosage, with a superior persistence for picaridin [29]. To maintain effectiveness than with the higher concentrations (>20%) of picaridin used in the field.

2.4 DEPA

N,N-diethyl-2-phenyl-acetamide (DEPA) is a repellent developed around the same time as DEET and repels a wide range of insects, but DEPA did not get its reputation. The repellency of DEPA has demonstrated almost similar to DEET against mosquito vectors as *Ae. aegypti*, *Ae. albopictus*, *An. stephensi*, and *C. quinquefasciatus* [13]. It has regained interest recently and could prove to be an important competitor to DEET especially in developing countries due to its low cost, \$25.40 per kg compared to \$48.40 per kg for DEET [30].

2.5 Insect repellent 3535

Learning from nature offered a molecule with an impressive performance in comparison to a natural and pure synthetic repellent solution called insect repellent 3535 (IR3535). Scientists got inspirations from nature for the development of the topical IR 3535 with the intention to create a molecule with optimized protection times and low toxicity. The naturally occurring amino acid β -alanine was used as a basic module, and the selected end groups were chosen to avoid toxicity and increase efficacy. IR 3535 was developed by Merck in 1970 and thus named as Merck IR3535; it has been available in Europe, but it was not available in the USA until 1999 [12]. IR3535 is used for humans and animals, as it is effective against mosquitoes, ticks, flies, fleas, and lice. Its chemical formula is $C_{11}H_{21}NO_3$, and its other names are ethyl-*N*-acetyl-*N*-butyl- β -alaninate, ethyl butylacetylaminopropionate (EBAAP), β -alanine, and *N*-acetyl-*N*-butyl-ethyl ester. The protection of IR 3535 may be comparable to DEET, but it requires frequent reapplication in every 6–8 h. IR3535 is found in products including Skin So Soft Bug Guard Plus Expedition (Avon, New York, NY) [31]. Although 20% IR 3535 provides complete protection against *Aedes* and *Culex* mosquitoes (up to 7–10 h), it offers lesser protection against *Anopheles* (about 3.8 h), which affects its application in malaria-endemic areas [13]. Several field studies were identified and indicated that IR 3535 is as effective as similarly, DEET in repelling mosquitoes of the *Aedes* and *Culex* genera but may be less effective than DEET in repelling anopheline mosquitoes; an uncontrolled field study of a controlled release formulation of IR 3535 reported that these formulations may provide complete protection against mosquito biting for 7.1–10.3 h [32].

2.6 Ethyl anthranilate

Ethyl anthranilate (EA) is a new member in the scope of entomology which drew a significant attention in repellent research in the recent years and is being considered as an improved alternative to DEET [13, 33]. It is a nontoxic, the US FDA approved volatile food additive. EA is novel and repellent against *Ae. aegypti*, *An. stephensi*, and *Cx. quinquefasciatus* as its ED₅₀ values of EA were 0.96, 5.4, and 3.6% *w/v*, respectively, and CPTs of EA, 10% *w/v*, throughout the arm-in-cage method were 60, 60, and 30 min, respectively. Moreover, its spatial repellency was found to be extremely effective in repelling all the three tested species of mosquitoes. EA provided comparable results to standard repellent DEPA. As a result, the repellent activity of EA is promising for developing effective, safe, and eco-friendly alternative to the existing harmful repellents for personal protection against different mosquito species [34].

2.7 Comparative efficacy of synthetic repellents

The comparative efficacy of synthetic repellents had been summarized [14] as follows: *Aedes* species demonstrated an aggressive biting behavior and *Ae. Aegypti*,

above all, proved to be tolerant to many repellent products. *Ae. albopictus* was easier to be repelled than *Ae. aegypti*. DEET is the most studied insect repellent; at higher concentrations, it presented superior efficacy against *Aedes* species, providing up to 10 h of protection. Although IR3535 and picaridin showed good repellency against this mosquito genus, their efficacy was on average inferior to that provided by DEET. Fewer studies have been conducted on the mosquito species *Anopheles* and *Culex*. The repellency profile against *Anopheles* species was similar for the four principal repellents of interest: DEET provided on average 5–11 h, IR 3535 4–10 h, picaridin 6–8 h, and *Citriodora* 1–12 h of protection, depending on study conditions and repellent concentration. *Culex* mosquitoes are easier to repel, and each repellent provided good protection against this species. DEET showed 5–14 h of protection and IR 3535 2–15 h, depending on product concentration, while the test proving the efficacy of picaridin and commercial products containing PMD was discontinued after 8 h of protection. To go over the main points, DEET remains probably the most efficient insect repellent against mosquitoes, effective against sensitive species as *Culex* as well as more repellent-tolerant species such as *Aedes* and *Anopheles*. Even though fewer studies have been conducted on these non-DEET compounds, picaridin and to some extent IR 3535 represent valid alternatives. Consequently, the choice of repellents could be adjusted somehow according to the profile of biting vectors at the travelers' destination.

3. Botanicals

Nature is an old unlimited source of inspiration for people [1, 11, 18, 35] as well as for scientific and technological innovations. Recently, global attention has been paid toward exploring the medicinal benefits of plant extracts [4, 11, 36, 37]. Repellents of natural origin are derived from members of the families as *Asteraceae*, *Cupressaceae*, *Labiatae*, *Lamiaceae*, *Lauraceae*, *Meliaceae*, *Myrtaceae*, *Piperaceae*, *Poaceae*, *Rutaceae*, *Umbelliferae*, and *Zingiberaceae*. They have been evaluated for repellency against various mosquito vectors, but few compounds have been found commercially. Increased curiosity in plant-based arthropod repellents was generated after the United States Environmental Protection Agency (US EPA) added a rule to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) in 1986 exempting compounds considered to be minimum hazardous pesticides [30]. Increased interest has also been driven by the rapid registration process of plant-based repellents by US EPA, which are often registered in less than a year, while the conventional pesticides are registered in an average of 3 years [30]. The public considers botanicals as safer and suitable alternative repellents; most of them are produced and distributed locally and appear on the market for only a short time. Even though many studies have shown that almost all registered commercial products based on botanical active ingredients offer limited protection and require frequent reapplication than even a low concentration of DEET-based repellents, the growing demand for natural alternative repellents in the community illustrates further need to evaluate new botanical repellents critically for personal protection against mosquitoes and mosquito-borne illnesses [7, 8, 13, 17]. The repellent activity of EOs includes some metabolites, such as the monoterpenes α -pinene, cineole, eugenol, limonene, terpinolene, citronellol, citronellal, camphor, and thymol that are repellents against mosquitoes; the sesquiterpene, β -caryophyllene, is repellent against *A. aegypti*, and phytol, a linear diterpene alcohol, is repellent against *Anopheles gambia*. Most of the arthropod-repellent compounds are oxygenated, having the hydroxyl group linked to a primary, secondary, or aromatic carbon. In some metabolites having a hydroxyl group linked to a tertiary carbon, as linalool,

α -terpineol, and limonene, the repellent activity is suppressed against *A. gambiae*, suggesting the likelihood that the type of carbon where the hydroxyl substitution is there modulates repellency. Most insect repellents are volatile terpenoids such as terpinen-4-ol. Other terpenoids can act as attractants. More information is widely discussed [7, 38], and chemical structures of some natural repellent compounds are shown in **Figure 2**.

3.1 PMD and lemon-scented eucalyptus

Compound *p*-menthane-3,8-diol (PMD) is derived from lemon-scented eucalyptus (*Eucalyptus citriodora*, *Myrtaceae*) leaves, and its importance as a repelling agent is increasing due to its good efficacy profile as well as its natural basis. PMD is a potent and commercially available repellent discovered in the 1960s via mass screening of plants for repellent activity, for instance, lemon eucalyptus and *Corymbia citriodora* (*Myrtaceae*) formerly known as *Eucalyptus maculata citriodora*. Lemon eucalyptus EO contains 85% citronellal and is already used in cosmetic industries due to its fresh smell. It was discovered when the waste distillate remaining after hydro-distillation of the EO was far more effective at repelling mosquitoes than the EO itself, and it provides very high protection from a broad range of insect vectors for several hours as well [7, 39]. The EO from *C. citriodora* also contains active constituents like citronella, citronellol, geraniol, isopulegol, and δ -pinene which play important roles in repelling both mosquitoes and ticks. Such compounds provide short-term repellency against mosquitoes, but PMD has a longer protection time than other plant-derived compounds because it is a monoterpene with low volatility than volatile monoterpenes found in most EOs and does not tend to evaporate rapidly after skin application [7, 8, 14].

There have been attempts to commercialize and market the insecticides/repellent products containing eucalyptus oil as such or based upon them. Crude eucalyptus oil was primarily registered as an insecticide and miticide in the USA in 1948, and 29 of such compounds have been registered in the USA until the year 2007 for use as natural insecticide/insect repellent/germicide. Only four products of them

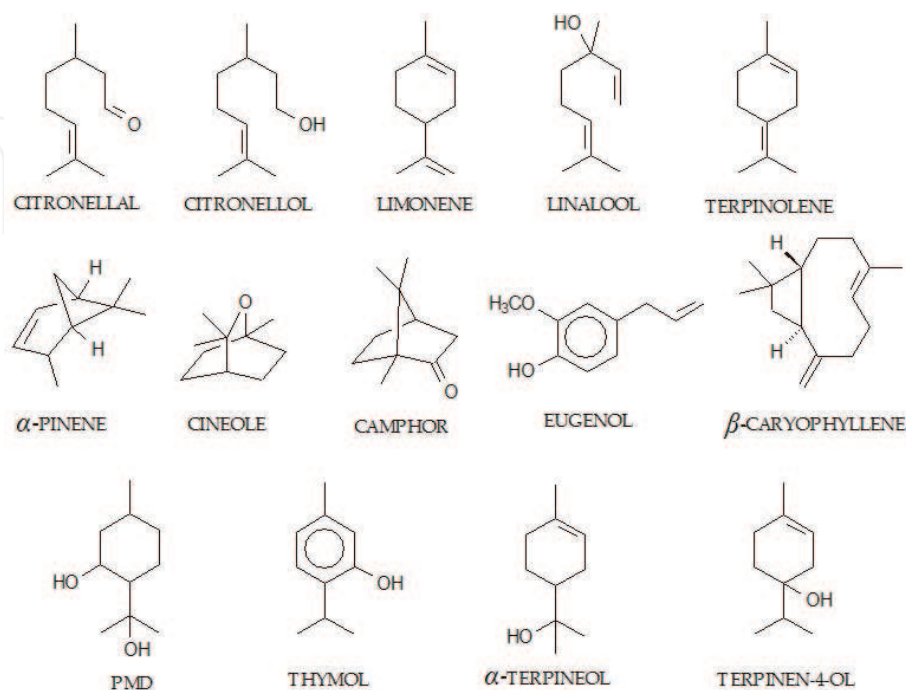


Figure 2.
 Chemical structures of some natural repellent compounds found in botanical species.

have been active, whereas 25 have been canceled. These include Citriondiol, Repel essential insect repellent lotion (two variants), Repel essential insect repellent pump spray, and Repel insect repellent 30 by the United Industrial Corp., USA. Some eucalyptus-based products include the following: Quwenling is successfully marketed as an insect repellent in China and provides protection against anopheles mosquitoes parallel to DEET and has exchanged the widely used synthetic repellent dimethylphthalate; Quwenling contains a mixture of PMD, citronellol, and isopulegone. Mosiguard Natural contains 50% eucalyptus oil, Buzz Away is a commercially available product in China based on citronellal, and MyggA1 Natural is based on PMD from lemon eucalyptus and is shown to repel ticks. More details are widely discussed [40].

3.2 Citronella

The name “Citronella” is derived from the French word “citronelle” around 1858. It was extracted to be used in perfumery and used by the Indian Army to repel mosquitoes at the beginning of the twentieth century and was then registered for commercial use in the USA in 1948. Today, citronella (5–10%) is one of the most widely used natural repellents on the market; such concentrations are lower than most other commercial repellents, whereas higher concentrations can cause skin sensitivity. Among plant-derived substances, products containing Citriondiol showed the most effective repellent profile against mosquitoes. EOs and extracts belonging to plants in the *Citronella* genus (Poaceae) are commonly used as ingredients of plant-based mosquito repellents, mostly *Cymbopogon nardus* that is sold in Europe and North America in commercial preparations [39]. Citronella contains citronellal, citronellol, geraniol, citral, α -pinene, and limonene giving an effect similar to that of DEET, but the oils rapidly evaporate causing loss of efficacy and leaving the user unprotected. Among plant-derived substances, products containing Citriondiol showed the most effective repellent profile against mosquitoes. For travelers heading to disease-endemic areas, citronella-based repellents should not be recommended, but if efficacious alternatives are prohibitively expensive or not available, the use of citronella to prevent mosquito bites may provide important protection from disease vectors. Even though citronella-based repellents only give protection from host-seeking mosquitoes for a short time (2 h), formulations could prolong such time (please see the formulation section).

3.3 Neem and methyl jasmonate

The aromatic plants of the *Meliaceae* family which include neem, *Azadirachta indica*, *Carapa procera*, *Melia azedarach*, *Khaya senegalensis*, and *Trichilia emetica* contain substances of the limonoid group and insecticidal and repellent effects on insects [18]. Neem provided a protection of 98.2% for 8 h against *An. darlingi*. Regardless of being not approved by US EPA for use as a topical insect repellent, neem is widely advertised as a natural alternative to DEET, and it has been tested for repellency against a wide range of arthropods of medical and veterinary importance. MiteStop®, based on a neem seed extract, had a considerable repellent effect on bloodsucking mosquitoes, tabanids, ceratopogonids, simuliids, as well as licking flies [41]. Several field studies from India have shown the very high efficacy of neem-based preparations, contrasting with findings of intermediate repellency by other researchers. However, these contrasting results may be due to differing methodologies and the solvents used to carry the repellents.

Methyl jasmonate (MJ) is derived from the nonvolatile jasmonic acid and has the ultimate vapor pressure for a repellent (0.001 mmHg at 25°C) which is quite higher

than DEET. It repels only *Cx. quinquefasciatus* but does not repel *Ae. aegypti*, *An. gambiae*, *Phlebotomus* flies, and *Glossina morsitans*, which restricts the application of MJ to *C. quinquefasciatus* mosquitoes only. On the other hand, MJ has been found to cause aversion in a number of ticks such as nymphal *I. ricinis* and *Hyalomma marginatum rufipes* Koch, etc. [30].

3.4 Essential oils

EOs are used against insects [20, 42–50] throughout the globe. EOs are distilled from members of the *Lamiaceae* (mint family), *Poaceae* (aromatic grasses), and *Pinaceae* (pine and cedar family). EOs could be used for farm animal protection against nuisance flies and lice [47]. Almost all of the botanical repellents are also used for food flavoring or in the perfume industry, indicating that they are safer than DEET. The most effective oils include thyme, geraniol, peppermint, cedar, patchouli, and clove that have been found to repel malaria, filarial, and yellow fever vectors for a period of 60–180 mins. Most of these EOs are highly volatile, and this contributes to their poor longevity as mosquito repellents. As a result, repellents containing only EOs in the absence of an active ingredient such as DEET should not be recommended as repellents for use in disease-endemic areas, whereas those containing high levels of EOs could cause skin irritation, especially in the presence of sunlight [39]. Although EOs effectively repel mosquitoes as irritants, repellents, antifeedants, or maskants, unfortunately, relatively few have been commercialized, despite being widely used in candles and as topical insect repellents. Botanical, herbal, or natural-based repellents include one or several plant EOs. These oils are considered safe by the EPA at low concentrations but provide a limited duration of protection against mosquitoes (<3 h). Citronella (discussed previously) is the principal and sometimes only active ingredient in many plant-based insect repellents [7]. Eucalyptus oil is used as an antifeedant mainly against biting insects as eucalyptus-based products used on humans as insect repellent can give protection from biting insects up to 8 h depending upon the concentration of the essential oil. Such repellent activity could be extended up to 8 days when eucalyptus EOs are applied on the clothes. Eucalyptus oil (30%) can prevent mosquito bite for 2 h; however, the oil must have at least 70% cineole content [40]. On the other hand, *E. citriodora* EO alone showed an insufficient protection against the three main mosquito species [14].

4. Safety of repellents

4.1 Safety of synthetic repellents

Insect repellents containing DEET are broadly used among populations. DEET should be used with caution as it may damage spandex, rayon, acetate, and pigmented leather and it could dissolve plastic and vinyl (e.g., eyeglass frames). Moreover, DEET damages synthetic fabrics and painted and varnished surfaces, precluding its use in bed nets and in many urban settings [51]. Being the gold standard of repellents, the safety profile of DEET is largely studied. There is an estimated 15 million people in the UK, 78 million people in the USA, and 200 million people globally that use DEET each year safely when it is applied to the skin at the correct dose indicated at the commercial preparation (in the case of it not being swallowed or rubbed into the mucous membranes). DEET has been used since 1946 with a tiny number of reported adverse effects, many of which had a history of excessive or inappropriate use of repellent. Its toxicology has been more closely

scrutinized than any other repellent, and it has been deemed safe for human use, including its use on children, pregnant women, and lactating women [39]. Even though insect repellents containing DEET are safe, some side effects have been described, mainly after inappropriate use such as dermatitis, allergic reactions, neurologic and cardiovascular side effects, as well as encephalopathy in children. In addition, there are a small number of reports of systemic toxicity in adults following dermal application. The safety profile in the second and third trimester of pregnancy has been well known through inspection of very low placental cord concentrations after maternal application of DEET, but animal models do not indicate any teratogenic effects. DEET also blocks mammalian sodium and potassium ion channels contributing to the numbness of lip following the application of DEET [13]. Approval for use in young children is a controversial issue between countries, with some recommending lower concentrations, whereas others suggesting that higher strengths can be used. However, the causation between the few reported cases of encephalopathy in children and the topical use of DEET cannot be supported by a good evidence base [14, 39].

When permethrin is impregnated appropriately in cloths and nets, toxicity fearfulness is minimal [52]. Although synthetic pyrethroids are utilized worldwide as active ingredients in MRs [15] due to their relatively low toxicity to mammals [53], inappropriate application at high doses initiates neurotoxic effects such as tremors, loss of coordination, hyperactivity, paralysis, and an increase in body temperature. Other side effects include skin and eye irritation, reproductive effects, mutagenicity, alterations in the immune system, etc. [13]. Recent studies also showed that some pyrethroids are listed as endocrine disruptors and possible carcinogens [53] and pyrethroids might cause behavioral and developmental neurotoxicity, with special concern revolving around infants and children, due to their potential exposure during a sensitive neurodevelopmental stage [54]. More evidence in the recent years indicates that pyrethroid insecticides can reduce sperm count and motility, cause deformity of the sperm head, increase the count of abnormal sperm, damage sperm DNA, induce its aneuploidy rate, affect sex hormone levels, and produce reproductive toxicity [55]. Moreover, an elevated concentration of transfluthrin in the gaseous phase during the indoor application of an electric vaporizer was detected, but they found inhalation risk of airborne transfluthrin was low. The exposure levels and potential risk of pyrethroids during the applications of other types of commonly used MRs remain unknown [53]. On the other hand, long-term exposure to pyrethroid-based MRs in indoor environments causes chronic neurotoxicity, for example, dysfunction of blood-brain barrier permeability, oxidative damage to the brain, [56] and cholinergic dysfunction which cause learning and memory deficiencies [57]. Even though ventilation through natural air exchange and conditioner dissipate of airborne pollutants, residues persisting in the air and/or on indoor surfaces could potentially cause continuous exposure to the residents.

US EPA-OPP's Biochemical Classification Committee classified IR 3535 as a biochemical in 1997, because it is functionally identical to naturally occurring beta-alanine in that both repel insects, the basic molecular structure is identical, the end groups are not likely to contribute to toxicity, and it acts to control the target pest via a nontoxic mode of action [58]. No reported toxicity has been made so far against IR 3535, and it induces less irritation to mucous membranes and exhibits safer oral and dermal toxicity than DEET which makes it an attractive alternative to DEET in disease-inflicted endemic regions [13]. The ester structure of the propionate grants essential advantages because of a short metabolic degradation and quick excretion as a simple water-soluble acid [58]. Picaridin has the advantage of being odorless and non-sticky or greasy. Moreover, unlike DEET, picaridin does not

damage plastics and synthetics. In some studies, picaridin induces no adverse toxic reactions in animal studies but exhibits low toxicity and less dermatologic and olfactory irritant in other studies. Consequently, picaridin's comparable efficacy to DEET and its suitability of application and favorable toxicity profile ranked it as an attractive option and unquestionably an acceptable alternative for protection against mosquitoes and other hematophagous arthropods to control the menace of vector-borne diseases in endemic areas [13]. DEPA does not show cytotoxicity or mutagenicity [59], thereby increasing its suitability in direct skin application. It also exhibits moderate oral toxicity (mouse oral LD₅₀ 900 mg/kg) and low to moderate dermal toxicity (rabbit and female mouse LD₅₀ of 3500 and 2200 mg/kg, respectively) [60]. Acute and subacute inhalation toxicity studies of DEPA have also been reported [61] which indicate its applicability as aerosol formulations. Indalone was an early synthetic repellent effective against both mosquitoes and ticks. It was even more effective than DEET; however, its chronic exposure induced kidney and liver damage in rodents which restricted its application [13]. EA is approved by the US FDA, WHO and European Food Safety Authority (EFSA) [62, 63]. Furthermore, EA has been listed in the "generally recognized as safe" [64] list by the Flavour and Extract Manufacturers Association (FEMA) [65]. EA does not damage synthetic fabrics, plastics, and painted and varnished surfaces which further widen the utility of EA in bed nets, cloths, and different surfaces in the endemic settings [14, 66].

4.2 Safety of plant-based repellents

Because many conventional pesticide products fall into disfavor with the public, botanical-based pesticides should become an increasingly popular choice as repellents. There is a perception that natural products are safer for skin application and for the environment, just because they are natural and used for a long time compared to synthetic non-biodegradable products [14]. In contrast to DEET, some natural repellents are safer than others, and plant-based repellents do not have this strictly tested safety evidence, and many botanical repellents have compounds that need to be used with caution [39]. PMD has no or very little toxicity to the environment and poses no risks to humans and animals. PMD has been developed and registered for use against public health pests and is available as a spray and lotion. Not much is known about the toxicity of eucalyptus oils; however, they have been categorized as GRAS by the US EPA. Further, the oral and acute LD₅₀ of eucalyptus oil and cineole to rat is 4440 mg/kg body weight (BW) and 2480 mg/kg BW, respectively, making it much less toxic than pyrethrins (LD₅₀ values 350–500 mg/kg BW; US EPA, 1993) and even technical grade pyrethrum (LD₅₀ value 1500 mg/kg BW) [40]. PMD is an important component of commercial repellents in the US and registered by US EPA and Canadian Pest Management Regulatory Agency in 2000 and 2002, respectively [13]. In contrary, lemon eucalyptus EO does not have US EPA registration for use as an insect repellent. PMD is the only plant-based repellent that has been advocated for use in disease-endemic areas by the Centers for Disease Control (CDC), due to its proven clinical efficacy to prevent malaria, and is considered to pose no risk to human health [39]. In 2005, the US Centers for Disease Control and Prevention made use of its influence by endorsing products containing "oil of lemon eucalyptus" (PMD), along with picaridin and DEET as the most effective repellents of mosquito vectors carrying the West Nile virus [67]. PMD provides excellent safety profile with minimal toxicity. In studies using laboratory animals, PMD demonstrated no adverse effects apart from eye irritation. It is safe for both children and adults as the toxicity of PMD is very low. However, the label indicates it should not be used on children under the age of 3 [7].

The safety of neem is extensively reviewed; azadirachtin is nontoxic to mammals and did not show chronic toxicity. Even at high concentrations, neem products were neither mutagenic nor carcinogenic, and they did not produce any skin irritations or organic alterations in mice and rats. On the other hand, reversible reproduction disturbances could occur due to the daily feeding of aqueous leaf extract for 6 and 9 weeks led to infertility of rats at 66.7 and 100%, respectively. Using unprocessed and aqueous neem-based products should be encouraged if applied with care. The pure compound azadirachtin, the unprocessed materials, the aqueous extracts, and the seed oil are safe to use even as insecticides to protect stored food for human consumption, whereas nonaqueous extracts turn out to be relatively toxic [8]. From the ecological and environmental standpoint, azadirachtin is safe and nontoxic to fish, natural enemies, pollinators, birds, and other wildlife. Azadirachtin is classified by the US EPA as class IV (practically nontoxic) [7, 8, 17] as azadirachtin breaks down within 50–100 h in water and is degraded by sunlight as the half-life of azadirachtin is only 1 day, leaving no residues. Safety and advantages of EOs are widely discussed [7, 8, 17, 39]. There is a popular belief that EOs are benign and harmless to the user. Honestly, increasing the concentration of plant EOs as repellents could increase efficacy, but high concentrations may also cause contact dermatitis. Some of the purified terpenoid ingredients of EOs are moderately toxic to mammals. Because of their volatility, EOs have limited persistence under field conditions. With few exceptions, the oils themselves or products based on them are mostly nontoxic to mammals, birds, and fish. Many of the commercial products that include EOs (EOs) are on the “*generally recognized as safe*” [64] list fully approved by the US FDA and EPA for food and beverage consumption. Moreover, EOs are usually devoid of long-term genotoxic risks, and some of them show a very clear antimutagenic capacity which could be linked to an anticarcinogenic activity. The prooxidant activity of EOs or some of their constituents, like that of some polyphenols, is capable of reducing local tumor volume or tumor cell proliferation by apoptotic and/or necrotic effects. Due to the capacity of EOs to interfere with mitochondrial functions, they may add prooxidant effects and thus become genuine antitumor agents. The cytotoxic capacity of the essential oils, based on a prooxidant activity, can make them outstanding antiseptic and antimicrobial agents for personal uses, that is, for purifying air, personal hygiene, or even internal use via oral consumption and for insecticidal use for the preservation of crops or food stocks. Some EOs acquired through diet are actually beneficial to human health [68, 69]. Eugenol is an eye and skin irritant and has been shown to be mutagenic and tumorigenic. Citronellol and 2-phenylethanol are skin irritants, and 2-phenylethanol is an eye irritant, mutagen, and tumorigenic; they also affect the reproductive and central nervous systems [30]. Hence, it is advised that EOs with toxic profile should be used for treating clothing rather than direct application to individual's skin [13]. Although EOs are exempt from registration through the US EPA, they can be irritating to the skin, and their repellent effect is variable, dependent on formulation and concentration. The previously mentioned safety and advantages designate that EOs could find their way from the traditional into the modern medical, insecticidal, and repellent domain.

5. Conclusions and challenges for future research

Several diseases transmitted by mosquitoes cause high losses of human and animal lives every year. DEET is considered as a “gold standard” to which other candidate repellents are compared; therefore, DEET is the most ever-present active ingredient used in commercially available repellents, with noteworthy protection

against mosquitoes and other biting insects. Unfortunately, the widespread use and effectiveness of commercial formulations containing DEET and other synthetic substances could lead to resistance [70, 71]. Some health and environmental concerns lead to the search for natural alternative repellents. The use of repellent plants has been used since antiquity [1], and it is the only effective protection available for the poor people against vectors and their associated diseases [71]. Ethnobotanical experience is passed on orally from one generation to another, but it needs to be preserved in a written form and utilized as a rich source of botanicals in repellent bioassays. Then again, the growing demand for natural repellents points up the further necessity to evaluate new plant-based products critically for personal protection against mosquitoes and mosquito-borne diseases [7, 8, 17, 18]. Regarding environmental and health concerns, plant-based repellents are better than synthetic molecules. Even though many promising plant repellents are available, their use is still limited; therefore, advance understanding of the chemical ecology of pests and the mode of repellency would be helpful for identifying competitor semiochemicals that could be incorporated into attractant or repellent formulations. There are numerous commercially available formulations enhancing the longevity of repellent, by controlling the rate of delivery and the rate of evaporation. Such formulations are very useful to people living in the endemic areas in the form of sprays, creams, lotions, aerosols, oils, evaporators, patch, canister, protective clothing, insecticide-treated clothing, and insecticide-treated bed nets [7, 8, 17]. The potential uses and benefits of microencapsulation and nanotechnology are enormous including enhancement involving nanocapsules for pest management and nanosensors for pest detection [7, 8]. Nanoparticles are effectively used to control larvae [72–76] and to repel adults of mosquitoes [77, 78].

Polymer-based formulations allow entrapping active ingredients and provide release control. Encapsulation into polymeric micro/nanocapsules, cyclodextrins, polymeric micelles, or hydrogels constitutes an approach to modify physicochemical properties of encapsulated molecules. Such techniques, applied in topical formulations, fabric modification for personal protection, or food packaging, have been proven to be more effective in increasing repellency time and also in reducing drug dermal absorption, improving safety profiles of these products. In this work, the main synthetic and natural insect repellents are described as well as their polymeric carrier systems and their potential applications [79]. Encapsulated EO nanoemulsion is prepared to create stable droplets to increase the retention of the oil and slow down release. The release rate correlates well to the protection time so that a decrease in release rate can prolong mosquito protection time. Microencapsulation is another way to slowly release the active ingredients of repellents. In laboratory conditions, the microencapsulated formulations of the EOs showed no significant difference with regard to the duration of repellent effect compared to the microencapsulated DEET used at the highest concentration (20%). It exhibited >98% repellent effect for the duration of 4 h, whereas, in the field conditions, these formulations demonstrated the comparable repellent effect (100% for a duration of 3 h) to Citriodiol®-based repellent (Mosiguard®). In both test conditions, the microencapsulated formulations of the EOs presented longer duration of 100% repellent effect (between 1 and 2 h) than non-encapsulated formulations [80]. Microencapsulation reduces membrane permeation of CO while maintaining a constant supply of the citronella oil [81]. Moreover, using gelatin Arabic gum microcapsules also prolonged the effect of natural repellents. In addition, the functionalization of titanium dioxide nanoparticles on the surface of polymeric microcapsules was investigated as a mean to control the release of encapsulated citronella through solar radiation. The results showed that functionalizing the microcapsules with nanoparticles on their surface and then exposing them to

	Repellent composition	Dose	Study variety	Mosquito spp.	Mean CPT	Protection		Reference
						%	Time interval	
Bio Skincare®	Natural oil of jojoba, rapeseed, coconut, and vit. E	1.2 g/arm	Arm-in-cage	<i>An. arabiensis</i>		100	3–4 h	[85]
BioUD® spray	7.75% 2-undecanone	1 ml/600 cm ²	Arm-in-cage	<i>Ae. aegypti</i>		52	6 h	[86]
						96.1	1 h	
						86.7	2 h	
						81.7	3 h	
						79.5	4 h	
						70.1	5 h	
						68.2	6 h	
	7.75% 2-undecanone	1 ml/600 cm ²	Field trial in North Carolina (USA)	<i>Ae. albopictus</i>		94.5	1 h	
						98.3	2 h	
						93.1	3 h	
						79.4	4 h	
						87.4	5 h	
						76.3	6 h	
	7.75% 2-undecanone	1 ml/600 cm ²	Field trial in North Carolina (USA)	<i>Ae. atlanticus/tormentor</i> (23.3%) <i>Psorophora ferox</i> (54.7%)		98.4	3 h	
						94.2	4 h	
						92.2	5 h	
						79	6 h	
			Field trial in Canada	<i>Ae. vexans</i> (32%) <i>Ae. euedes</i> (29.3%) <i>Ae. stimulans</i> (15.3%)		95.5	4 h	
						95.6	6 h	
Bite Blocker® lotion	Glycerin, lecithin, vanillin, oils of coconut, geranium, and soybean (2%)	1 ml/650 cm ²	Arm-in-cage	<i>Ae. albopictus</i> <i>Cx. nigripalpus</i>	5.5 h 8.3 h			[87]
Bite Blocker Xtreme®	3% soybean oil 6% geranium oil 8% castor oil		Field trial in Canada	<i>Ae. vexans</i> (32%) <i>Ae. euedes</i> (29.3%) <i>Ae. stimulans</i> (15.3%)		93.9	4 h	[86]
						53.7	6 h	
Buzz Off Insect Repellent®	Natural plant extract	1 g/forearm	Arm-in-cage	<i>Ae. aegypti</i> <i>Ae. vigilax</i> <i>Cx. Annulirostris</i> <i>Cx. quinquefasciatus</i>	0 min 0 min 160 min 50 min			[88]
Baygon®	Oils of canola, eucalyptus, peppermint, rosemary, and sweet birch	1 ml/650 cm ²	Arm-in-cage	<i>Ae. albopictus</i> <i>Cx. nigripalpus</i>	0.2 h 4.7 h			[87]

	Repellent composition	Dose	Study variety	Mosquito spp.	Mean CPT	Protection		Reference
						%	Time interval	
Citronella candles	3% citronella		Field trial in Canada	<i>Aedes</i> spp.		42.3		[89]
Citronella incense	5% citronella		Field trial in Canada	<i>Aedes</i> spp.		24.2		[89]
GonE!®	<i>Aloe vera</i> , camphor, menthol, oils of eucalyptus, lavender, rosemary, sage, and soybean	1 ml/650 cm ²		<i>Ae. albopictus</i> <i>Cx. nigripalus</i>	0.0 h 2.8 h			[87]
Green Ban for People®	Citronella 10%, peppermint oil 2%		Arm-in-cage	<i>Ae. aegypti</i>	14 min			[90]
Herbal Armor®	Citronella 12%, peppermint oil 2.5%, cedar oil 2%, lemongrass oil 1%, geranium oil 0.055		Arm-in-cage	<i>Ae. aegypti</i>	18.9 min			[90]
Kor Yor 15 DEET lotion®	DEET 24%, dimethylphthalate 24%	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	3 h			[91]
	DEET 24%, dimethylphthalate 24%	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	3 h			[92]
MeiMei® cream	Citronella and geranium oils		Indoor test	<i>Ae. aegypti</i>		97 97 85 44 27	30 min 50 min 70 min 90 min 120 min	[93]
	Citronella and geranium oils		Field trial in South Korea	<i>Aedes</i> (7.8%) <i>Armigeres</i> (5.9%) <i>Anopheles</i> (42.2%) <i>Culex</i> (44.1%)		90 57 56 34	30 min 90 min 150 min 210 min	[94]
Mistine censor®	IR 3535 12%, rosemary, lavender, and eucalyptus	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	1 h			[91]
	IR 3535 12%, rosemary, lavender, and eucalyptus	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	1 h			[92]
Mospel®	Clove oil 10% Makaen oil 10%	1 g/600 cm ²	Arm-in-cage	<i>An. stephensi</i>	4–5 h			[95]
		1 g/lower leg	Walk-in exposure room test		7–8 h			

	Repellent composition	Dose	Study variety	Mosquito spp.	Mean CPT	Protection		Reference
						%	Time interval	
MosquitoSafe®	Geraniol 25%, mineral oil 74%, aloe vera 1%	1 ml/650 cm ²	Arm-in-cage	<i>Ae. albopictus</i>	2.8 h			[87]
Neem Aura®	Aloe vera, extract of barberry, chamomile, goldenseal, myrrh, neem, and thyme; oil of anise, cedarwood, citronella, coconut, lavender, lemongrass, neem, orange, rhodium wood	1 ml/650 cm ²	Arm-in-cage	<i>Ae. albopictus</i> <i>Cx. nigripalpus</i>	0.2 h 4.2 h			[87]
Odomos® cream	Advanced Odomos (12% N,N-diethylbenzamide)	8 mg/cm ²	Arm-in-cage (Duration of the test: 4 h)	<i>Cx. nigripalpus</i>	3.8 h			[96]
		10 mg/cm ²			>4 h	100		
		10 mg/cm ²		<i>Ae. aegypti</i>	4 h	96.5		
		12 mg/cm ²			>4 h	100		
	Advanced odomos	10 mg/cm ²	Field trial in India Duration of the test: 11 h	<i>An. culicifacies</i> <i>An. stephensi</i> <i>An. annularis</i> <i>An. subpictus</i>	11 h	100		
		10 mg/cm ²		<i>Cx. quinquefasciatus</i>	9 h	98.8		
		10 mg/cm ²		<i>Ae. aegypti</i>	6.2 h	92.5		
Raid Dual Action and Raid Shield	transfluthrin-based spatial repellent products		Laboratory (wind tunnel) and	<i>Aedes aegypti</i>		95 and 74		[97]
			semi-field (outdoor enclosure) in Florida			88 and 66		

Repellent composition	Dose	Study variety	Mosquito spp.	Mean CPT	Protection		Reference
					%	Time interval	
Repel Care® Turmeric oil 5% <i>E. citriodora</i> 4.5%	2 ml/750 cm ²	Field trial in Thailand (duration of the test: 9 h)	<i>Ae. aegypti</i> (1.2%) <i>Others</i> (<1%) <i>Cx. vishnui</i> (77.1%) <i>Cx. quinquefasciatus</i> (13.8%) <i>Cx. gelidus</i> (3.4%) <i>Cx. tritaeniorhynchus</i> (1.6%)		100		
		Duration of the test: 8 h	<i>Ae. albopictus</i> (99.9%) <i>Ar. subalbatus</i> (0.01%)		100 96.9 92.4 91.8		
		Arm-in-cage	<i>Ae. aegypti</i>	1 h			[92]
Sketolene® lotion	DEET, <i>E. citriodora</i> oil 15%	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	3 h		[92]
Soffell® (citronella oil)	DEET 13%, citronella oil	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	4 h		[92]
Soffell® (floral fragrance)	DEET 13%, geranium			4 h			
Soffell® (fresh fragrance)	DEET 13%, orange			4 h			
Soffell® lotion	DEET, <i>E. citriodora</i> oil 15%	0.1 ml/30 cm ²	Field trial in Thailand (duration of the test: 120 min)	<i>Ae. gardnerii</i> <i>Ae. lineatopennis</i> <i>An. barbirostris</i> <i>Cx. Tritaeniorhynchus</i> <i>Cx. gelidus</i>	100	(120 min)	[91]

	Repellent composition	Dose	Study variety	Mosquito spp.	Mean CPT	Protection		Reference
						%	Time interval	
Sumione®	Metofluthrin-treated emanators	900-cm ² paper fan emanators impregnated with 160 mg metofluthrin	Field trials in PA, USA	<i>Aedes canadensis</i>		85–100		[98]
		4000-cm ² paper strip emanators impregnated with 200 mg metofluthrin		Laboratory-reared <i>Aedes aegypti</i>		89–91		
		Metofluthrin-impregnated paper strip emanator	In Florida	<i>Ochlerotatus</i> spp.		91–95		
		Metofluthrin-impregnated paper strip emanator	In Washington State	<i>Aedes vexans</i>		95–97		
SunSwat®	Oils of bay, cedarwood, citronella, goldenseal, juniper, lavender, lemon peel, patchouli, pennyroyal, tansy, tea tree, and vetiver	1 ml/650 cm ²	Arm-in-cage	<i>Ae. albopictus</i> <i>Cx. nigripalus</i>	0.2 h 4.2 h			[87]
Tipskin®	Bergamot oil, citronella oil, camphor oil, and vanillin	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	0 h			[91]
	Bergamot oil, citronella oil, camphor oil, and vanillin	0.1 ml/30 cm ²	Arm-in-cage	<i>Ae. aegypti</i>	0.5 h			[92]
OFF! Clip-On®	Metofluthrin		Field study in USA	<i>Ae. albopictus</i> and <i>Ae. taeniorhynchus</i>	3 h	70 and 79		[99]
				<i>Anopheles quadrimaculatus</i> , <i>Culex erraticus</i> , and <i>Psorophora columbiae</i>		Up to 84		[100]
Mosquito Cognito®	Linalool			<i>Anopheles quadrimaculatus</i> , <i>Culex erraticus</i> , and <i>Psorophora columbiae</i>		Up to 84		[100]
No-Pest Strip®	Dichlorvos							[100]
Thermacell®	d-cis/trans allethrin							[100]

Table 1.
Commercial mosquito-repellent products.

ultraviolet radiation effectively increased the output of citronella into the air for repelling the mosquitoes without human intervention, as the sunlight works as a release activator [82].

It is recommended to use US EPA-registered insect repellents including one of the active ingredients: DEET, Picaridin, IR3535, Oil of lemon eucalyptus (OLE), Para-menthane-diol (PMD), and 2-undecanone. Synthetic MRs are applied for years but induced some safety and environmental concerns; as a result, the advancement in the development of repellents from the botanical origin is encouraged. But some obstacles are hindering botanical repellents which as the source availability, standardization, commercialization, and analyses in order to certify the efficacy and safety [7]. Commercially available repellents are provided in **Table 1**. For saving time and efforts, a high-throughput chemical informatics screen via a structure-activity approach, molecular-based chemical prospecting [83], as well as computer-aided molecular modeling [84] would accelerate the exploration of new environmentally safe and cost-effective novel repellents which activated the same chemosensory pathways as DEET at a fairly shorter time and lower costs [13]. The selection of various repellents could be tailored along with the profile of safety concerns and biting vectors at the travelers' and military destinations by reducing annoyance and the incidence of illness. The use of these technologies to enhance the performance of natural repellents may revolutionize the repellent market and make EOs a more viable option for use in long-lasting repellents. Green technologies and cash cropping of repellent plants afford a vital source of income for small-scale farmers and producers in developing countries and raise the national economy. Moreover, in some developing countries where tourism is a chief source of national income, the use of repellents would increase the pleasure and comfort of tourists. Finally, much faster work needs to be done to discover new and safe repellents for personal protection from mosquitoes.

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