

Chemical Advances in Mosquito Repellents

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Mosquito-borne diseases, such as malaria, dengue, and Zika, continue to pose significant public health challenges worldwide, particularly in tropical and subtropical regions. The common types of mosquitoes present in the environment are as shown in Fig.1.

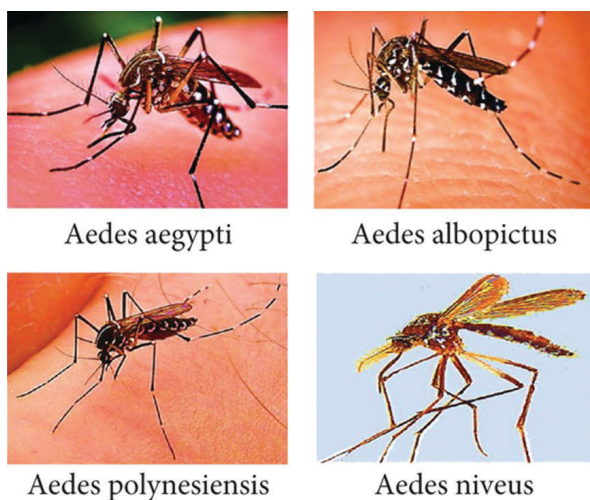


Figure 1. Most common types of mosquitoes in the environment

This review article delves into the intricate chemistry of mosquito repellents, offering a detailed examination of their molecular structures, mechanisms of action, and the latest advancements in repellent technologies. It explores synthetic pathways and the challenges in creating effective repellents, compares the stability and efficacy of natural versus synthetic compounds, and discusses the environmental impact and safety concerns associated with various repellent formulations.

The control of mosquito populations and the prevention of bites are critical in reducing the transmission of these pathogens. Chemical repellents have long been the primary means of protection against mosquito bites, with various synthetic and natural compounds developed to mitigate mosquito attraction. Despite the effectiveness of many conventional repellents, there remains a growing need for safer,

more sustainable alternatives due to concerns about toxicity, environmental impact, and the development of resistance in mosquito populations.

Chemical composition of repellents

Mosquito repellents typically contain a range of active chemical ingredients that disrupt the host-seeking behavior of mosquitoes. DEET, N,N-diethyl-meta-toluamide, (1) shown in Fig. 2 remains one of the most widely used synthetic compounds due to its broad efficacy and prolonged protection time [1].

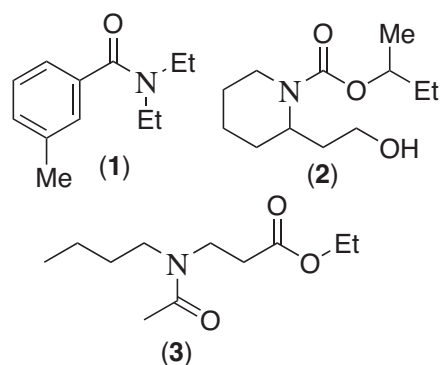


Figure 2. Structures of DEET (1), picaridin (2) and IR3535 (3)

Studies suggest that (1) works by confusing the olfactory receptors of mosquitoes, making it difficult for them to locate a host [1,2]. Other commonly used synthetic compounds include Picaridin or Icaridin (2), known for its lower skin irritability and comparable efficacy to DEET, and IR3535, ethyl butylacetylaminopropionate, (3) which has shown similar results with less persistence on the skin [3]. Increasingly, natural repellents such as citronella, lemongrass oil, eucalyptus oil, and neem oil are incorporated into formulations due to their mosquito-repelling properties and lower toxicological profiles [4]. The active compounds in these essential oils - like citronellal, eucalyptol, and linalool - act on the mosquito's olfactory and sensory neurons to produce

a repellent effect [5]. However, these natural products typically require higher concentrations and more frequent application than synthetic repellents, as they tend to evaporate quickly and provide shorter protection durations [3].

Formulation chemistry

The formulation chemistry of mosquito repellents focuses on optimizing the delivery, stability, and efficacy of active repellent ingredients. Emulsions, aerosols, lotions, gels, and sprays are among the most common formulations, each requiring different chemical considerations to ensure effective release and prolonged action of the active compounds, such as DEET and essential oils [1]. The stability of these active ingredients is a critical factor, as they must remain effective under varying environmental conditions, particularly temperature and humidity. Solvents and carriers, such as alcohol or cyclomethicone, are often included to improve solubility, facilitate even distribution, and enhance skin absorption without causing irritation [2]. Emulsifiers and stabilizers like lecithin and glyceryl stearate are used to create uniform mixtures, especially in water-based formulations, improving consistency and ease of application [3].

Encapsulation techniques, such as microencapsulation and nano-emulsion, have also been explored to provide controlled release of repellents over time, increasing the duration of mosquito protection while minimizing the evaporation of volatile components like essential oils [4,5]. Such advanced formulation strategies help in balancing potency, longevity, and user comfort, making repellents more convenient and effective for consumers.



Figure 3. Some mosquito repellents available in the market

Synthesis of repellent molecules

The synthesis of mosquito repellent molecules typically aims to enhance the activity, stability, and compatibility of these compounds in various formulations. DEET (1), the most common synthetic repellent, is synthesized through the acylation of meta-toluic acid with diethylamine, forming an amide linkage that helps block mosquito olfactory responses to human skin odors [1]. Another synthetic repellent, Picaridin (2), is derived from the piperidine ring, involving a multistep process that introduces a hydroxyethyl side chain, which provides both long-lasting efficacy and low skin irritation [2]. IR3535 (3), an ester-based repellent inspired by the natural amino acid structure of beta-alanine, is synthesized by combining an amino acid backbone with an ester linkage, resulting in a compound that is effective yet environmentally benign [3]. Recent research has focused on semi-synthetic methods to produce terpene-based repellents, such as isolongifolanone (4) (Fig. 4), which is derived from natural sources like pine oil through processes like catalytic hydrogenation. This semi-synthetic approach reduces the environmental footprint while retaining effective mosquito-repelling properties [4,5]. The structural diversity in these synthetic molecules allows for a range of functional groups and linkages, which are designed to interfere with the sensory receptors of mosquitoes in various ways, enhancing overall repellent performance.

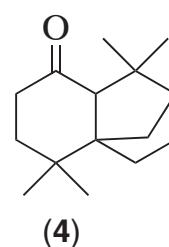


Figure 4. Structure of isolongifolanone (4)

Natural vs synthetic repellents

Table 1 demonstrates the key aspects of natural and synthetic mosquito repellents, including efficacy, duration, safety, and environmental impact.

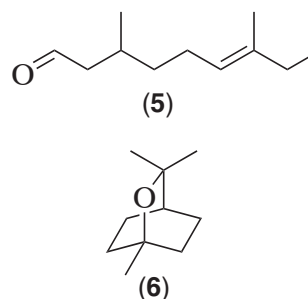
Table 1. Comparison of natural and synthetic repellents

Aspect [References]	Natural Repellents	Synthetic Repellents
Examples [1-4]	Citronella, Eucalyptus oil, Neem oil	DEET, Picaridin, IR3535
Efficacy [1-2]	Effective but generally lower than synthetic repellents	Highly effective with consistent protection
Duration [2,5]	Shorter protection time; requires frequent reapplication	Long-lasting, providing several hours of protection
Mode of Action [1,4,5]	Masks human odors, deterring mosquitoes	Blocks mosquito olfactory receptors from detecting skin odors
Skin Safety [3,4]	Generally safer, lower irritation risk	May cause skin irritation (DEET); Picaridin is gentler
Environmental Impact [1,3]	Biodegradable & ecofriendly	Persistent in environment, may impact water sources (DEET)
Cost [2,4]	Often lower; widely available	Generally, more expensive to produce
Volatility [3,5]	High volatility, tends to evaporate quickly	Lower volatility, especially with formulations like Picaridin

Chemical sensing and mosquito behavior

Mosquitoes rely on highly sensitive chemical sensing mechanisms to locate human hosts, with specific olfactory receptors in their antennae that detect carbon dioxide, body heat, and skin odors. These receptors play a crucial role in enabling mosquitoes to sense and target certain compounds, such as lactic acid and other volatiles, which are characteristic of human scent [6]. Repellents like DEET interfere with these olfactory receptors, masking the human scent or creating confusing signals that disrupt the mosquito's ability to detect and approach a host [7]. Studies have shown that DEET binds to certain odorant receptors, reducing the attraction of mosquitoes to skin odors, while other repellents, such as citronella (5) and eucalyptol (6), create a temporary barrier by overwhelming the mosquitoes' olfactory systems with strong, volatile compounds [8].

The structures of citronellal (5) present in citronella oil and eucalyptol (6) present in eucalyptus oil are shown in Fig. 5.

**Figure 5.** Structures of citronellal (5) and eucalyptol (6)

Picaridin, a synthetic repellent, also affects olfactory signaling by inhibiting receptors that are involved in recognizing human-derived odor cues [9]. These molecular interactions with olfactory receptors significantly influence mosquito behavior, reducing the likelihood of mosquito bites and thereby playing a critical role in the efficacy of repellents [10].

Resistance and adaptation

Over time, mosquitoes have shown the ability to adapt to various chemical repellents, potentially leading to decreased efficacy and even resistance.

Studies indicate that prolonged exposure to repellents like DEET may induce changes in mosquito behavior and physiology, allowing them to bypass or tolerate the repellent's effects. For instance, *Aedes aegypti* mosquitoes have been observed to reduce their avoidance response to DEET after repeated exposure, suggesting a form of desensitization to its active compounds [11]. Additionally, genetic studies reveal that certain mosquito populations may develop mutations in their olfactory receptors, which alter their sensitivity to chemical repellents, thus enabling these mosquitoes to detect human odors despite the presence of repellents [12]. Cross-resistance is also a concern, as adaptation to one repellent could reduce sensitivity to other related compounds. For example, mosquitoes exposed frequently to DEET may also exhibit reduced avoidance to structurally similar repellents like Picaridin [13]. This growing evidence underscores the need for continuous research to develop novel repellent formulations that can counteract potential resistance mechanisms and remain effective in mosquito control [14,15].

Safety and toxicology

The safety and toxicological effects of mosquito repellents are critical considerations, especially given their widespread use for personal protection against vector-borne diseases. Synthetic repellents like DEET and Picaridin have been extensively studied and are generally considered safe for use when applied according to guidelines; however, they are not without potential risks. DEET, for example, is highly effective but has been associated with skin irritation, neurotoxicity in rare cases, and potential environmental persistence, raising concerns for both human health and ecosystems [16]. Although typically rare, neurotoxic effects have been reported in cases of over-application or accidental ingestion, particularly in children [17]. Picaridin is known to be less irritating to the skin and has a lower toxicity profile, making it a preferable alternative for some users, but it still carries a risk of mild side effects [18]. Natural repellents, such as citronella and eucalyptus oils, are perceived as safer and are less likely to cause skin irritation, yet their safety profile is complicated by their high volatility, which can lead to eye or respiratory irritation with overuse

[19]. Evaluating the balance between efficacy and safety remains crucial for repellent selection, as higher concentration formulations, regardless of repellent type, generally increase the risk of adverse effects [20].

Environmental impacts of repellent chemicals

The environmental impact of mosquito repellent chemicals is an important concern, especially with widespread usage in areas affected by vector-borne diseases. Synthetic repellents like DEET and Picaridin, though effective, have been shown to persist in the environment, posing risks to aquatic ecosystems. Studies indicate that DEET can contaminate water sources, with detectable residues found in freshwater environments, potentially affecting aquatic organisms such as fish and amphibians [21]. The compound has been shown to be toxic to certain species, disrupting their behavior and reproductive systems [22]. Similarly, while Picaridin is considered less persistent than DEET, it can still accumulate in water and soil, raising concerns over its long-term environmental effects [23]. On the other hand, natural repellents like citronella and eucalyptus oil, though biodegradable, still pose risks due to their high volatility and potential for air and water pollution when used in large quantities. Citronella, in particular, can contribute to air pollution in confined spaces and cause respiratory irritation in sensitive individuals [3]. Understanding and mitigating the environmental impacts of repellent chemicals remains essential for ensuring that their benefits in controlling mosquito populations do not come at a greater ecological cost [24].

Conclusion

In conclusion, mosquito repellents play a crucial role in reducing the spread of vector-borne diseases by effectively preventing mosquito bites. Both synthetic and natural repellents have been developed and extensively studied for their efficacy and safety. While synthetic repellents such as DEET and Picaridin have proven to be highly effective, their environmental impact and potential for resistance in mosquito populations raise important concerns that warrant ongoing research. Natural repellents, though generally considered safer for both humans and the environment, often have limited

duration and efficacy. The development of new repellent formulations, including those that combine natural and synthetic ingredients, holds promise for enhancing efficacy while minimizing adverse effects. Furthermore, a better understanding of the chemical interactions between repellents and mosquito behavior, as well as their environmental impacts, is essential for optimizing their use. Ultimately, balancing the need for effective mosquito control with environmental and safety considerations will be key to developing sustainable, long-term solutions for vector management. Continued innovation and research into alternative repellents and resistance management strategies are necessary to ensure that these products remain effective in the fight against mosquito-borne diseases.

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