Next-gen insect repellents to combat mosquito-borne diseases

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Anopheles gambiae mosquito, feeding on blood. Credit: James Gathany, Centers for Disease Control and Prevention

Nearly 700 million people suffer from mosquito-borne diseases—such as malaria, West Nile, Zika and dengue fever—each year, resulting in more than 1 million deaths. Increasingly, many species of mosquitoes have become resistant to the popular pyrethroid-based insecticides. Today, researchers report a new class of mosquito repellents based on naturally occurring compounds that are effective in repelling mosquitoes with potentially fewer environmental side effects than existing repellents.

The scientists will present their research today at the 256th National Meeting & Exposition of the American Chemical Society (ACS).

"Our new repellents are based on how nature already works," Joel R. Coats, Ph.D., says. "For example, citronella, a spatial repellent that comes from lemongrass, contains naturally occurring essential oils that have been used for centuries to repel mosquitoes. But citronella doesn't last long and blows away easily. Our new, next-generation spatial repellents are variations of natural products that are longer-lasting and have greater repellency."

Coats and graduate students James S. Klimavicz and Caleb L. Corona at Iowa State University in Ames have been synthesizing and testing hundreds of compounds against mosquitoes. They knew that sesquiterpenoids, which are found in many plants, are effective insect repellents, but these large molecules are difficult to isolate from plants and hard to make and purify in the laboratory.

Because of the challenges of synthesizing sesquiterpenoids, Coats' team designed their repellents using smaller, less complex, easily obtainable molecules—monoterpenoids and phenylpropanoid alcohols with known, short-term repellent activities against insects. By modifying these compounds chemically, they produced new potential repellents with higher molecular weights, making them less volatile and longer-lasting. Klimavicz has synthesized more than 300 compounds, the most effective of which are α-terpinyl isovalerate (a natural compound), citronellyl cyclobutanecarboxylate and citronellyl 3,3-difluorocyclobutanecarboxylate.

To determine the compounds' effectiveness as repellents against mosquitoes, Corona tests them in a tubular chamber developed in the Coats laboratory. The chamber has filter papers at either end. One filter paper has nothing on it; the other has the synthesized repellent applied. Then mosquitoes—raised in the Iowa State University medical entomology lab—are introduced into the chamber. Corona uses time-lapse photography and in-person monitoring over 2.5 hours to document whether the mosquitoes migrate away from the candidate repellents. The researchers are currently exploring computer tracking of mosquitoes using video footage to gain a better understanding of mosquito repellency and behavior when exposed to these compounds.

With this method, the researchers tested the repellents with *Culex pipiens*, the northern house mosquito, which is most closely linked to West Nile transmission in the Midwestern U.S.; *Aedes aegypti*, the yellow fever mosquito which is also known to transmit the Zika and dengue viruses; and *Anopheles gambiae*, which transmits malaria.

"We think the mechanism of our terpene-based repellents, which try to mimic what nature does, is different from that of the pyrethroids," which many mosquito species have become resistant to, Coats says. "We believe these 'next-gen' spatial repellents are new tools that could provide additional protection against mosquitoes in treated yards, parks, campgrounds, horse stables and livestock facilities. Our next step is to understand more precisely how the repellents biologically affect the mosquitoes."

More information: Next-gen biorational spatial repellents, the 256th National Meeting & Exposition of the American Chemical Society (ACS).

Abstract
Among possible new tools to use against vectors, spatial repellents represent a category of tools that provide additional protection, especially against mosquitoes. In yards, parks, campgrounds, horse stables, and livestock facilities, spatial repellents can deter flies and mosquitoes from entering the treated area. Many personal or local uses of spatial repellents involve burning of a pyrethroid coil or otherwise emitting a volatile pyrethroid insecticide. Emitting oil of citronella is the primary alternative to the pyrethroids. Our lab has synthesized a series of biorational derivatives of natural terpenes to create repellents that provide physicochemical and biological properties that are improvements over citronella and other terpene repellents. Pyrethroid spatial repellents work well in some cases but are less effective against pyrethroid-resistant strains of mosquitoes. Some pyrethroid spatial repellents cause mosquito knockdown and mortality, which adds to their current efficacy, but potentially contributes to evolving of pyrethroid-resistance in a mosquito population. The mechanism of repellent action for terpenes is likely different from that of pyrethroids. The advanced terpenes could be valuable spatial repellents when used in conjunction with other more traditional tools.

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