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A Conversation with Kumudini Meepagala

Janet Pelley

The natural products chemist says plant compounds could repel Zika-bearing mosquitoes more effectively than DEET.

The spread of the Zika virus is raising fears that the virus's most heartbreaking consequence—babies with microcephaly born to infected mothers—will affect the U.S. and other countries as it has affected Brazil. The virus hitches a ride with *Aedes aegypti* mosquitoes, whose preference for biting humans makes them an ideal vector for transferring virus from one victim to another.

Repellents are the first line of defense against mosquito bites, but some studies suggest that the most popular repellent, DEET, damages the central nervous system of insects such as honeybees, as well as mammals. Searching for mosquito repellents without worrying side effects, Kumudini Meepagala, a natural products chemist with the U.S. Department of Agriculture in Mississippi, recently isolated and modified a plant compound that works better than DEET. She spoke to Janet Pelley about how she pulled the natural repellent out of Texas torchwood (*Amyris texana*), a shrub in the citrus family.

How did you know that Texas torchwood would produce a repellent?

Smart guessing starts by looking at the scientific literature and folk remedies. In our study, we noted that American Indians used torchwood because the plant has a lot of oily compounds that burn easily. And the citrus family is known for being a rich source of secondary metabolites that are insect repellent. A botanist colleague collected the torchwood for me from Cameron County in Texas. You don't have to go to the Amazon to collect biologically active plants—some are right here in your backyard.

Out of all the active compounds in torchwood, how did you home in on just the mosquito-repelling ones?

We conducted a systematic isolation. You grind up plant leaves and extract compounds using a series of solvents such as hexane, ethyl acetate, and methanol. Then we fractionate each extract, such as the ethyl acetate portion, in a silica gel column. If you're lucky, you can get a pure substance from this method.

Then we send the substances to the bioassay team members at the USDA labs in Gainesville, Florida. There, my colleague Ulrich Bernier recruits human volunteers to wear a patch containing the substance on their arm and to stick that arm into a cage with 500 starving female *Aedes* mosquitoes. If the volunteers get fewer than five bites in one minute, the compound passes. We have gotten some good hits. One of the most promising is a chromene amide.

So I could just spray this chromene amide on my skin before a hike in the woods?

No, we actually modified the natural molecule for several reasons. Sometimes, just a tiny little modification can get you a vastly different activity. For example, the natural chromene compound is an amide, but when we modified it to an alcohol derivative, it was much more active and long-lasting. In addition, it's important to find a method to synthesize these compounds in the lab because if you want to market this product, you cannot cut down all these torchwood shrubs to make it. Fortunately, we were able to synthesize this chromene analog and made kilograms of it in our lab.

That sounds like a lot of work. Why not just stick with DEET?

Our research for better mosquito repellents started as part of a program with the U.S. Armed Forces Pest Management

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Board. Soldiers want a repellent that lasts longer than DEET, which at most remains active for 2 days at the concentrations that soldiers use. The chromene analog protects against mosquitoes for 6 days at the same concentration. Also, we found that when we combined the chromene analog with DEET, the mixture repelled mosquitoes better than the sum of the two individual compounds. That means you could use less of each repellent.

In addition, some researchers have raised concerns that excessive doses of DEET affect the nervous system, but we don't know that conclusively.

Some countries, like Canada, have restricted use of DEET. How do you know that the chromene analog will be safe to use?

We've done some initial toxicology tests on rabbits and mice, and the results so far have been promising. But we have to do more tests to ensure that the chromene analog is nontoxic when inhaled and that it won't kill fish or insects such as honeybees.

Just because a compound is plant-based doesn't mean it's safe for the environment. For instance, the insecticide permethrin is a modified natural product from chrysanthemum plants, but it is toxic to fish and bees.

How have your life experiences informed your understanding of mosquito-borne disease?

I'm from Sri Lanka, and after the monsoon season, the mosquito eggs that have been hiding in the sand hatch into larvae. The mosquito populations go up, and always there's a Dengue fever outbreak. If I use repellent, it will prevent the mosquito from biting me. But if someone else doesn't use repellent, and the mosquito gets a blood meal from that person, the mosquito can produce eggs. If you don't kill the new generation coming up, then that will not end the cycle of the mosquito population. Only using repellents will not solve the problem of mosquito-borne disease.

I think an effective mosquito control strategy needs to be based on area-wide control methods using larvicides, adulticides, and repellents. Our most recent paper showed that chromene analogs can act as all three, and some of the larvicidal activity is on insecticide-resistant mosquito species. That looks promising.

Janet Pelley is a freelance contributor to Chemical & Engineering News, the weekly newsmagazine of the American Chemical Society. Center Stage interviews are edited for length and clarity.

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