Study upends 'dogma' on malaria drug component

9 April 2019, by Mick Kulikowski

Rika Judd and De-Yu Xie with A. annua plants in NC State's Phytotron. Credit: De-Yu Xie.

Mosquitoes won't fly anywhere near the sweet wormwood herb (Artemisia annua), so it makes perfect sense that a chemical compound produced by the plant has become the first line of treatment against malaria.

Now, a new North Carolina State University study shows that this plant-synthesized compound – artemisinin – can be produced more readily in the plant than previously understood, hastening the need to revise current scientific dogma about how and where it is produced in the plant and opening the door for new techniques to provide more stable production practices in the future.

At issue is the availability of artemisinin, which is produced by A. annua. The herb grows natively in China and has for thousands of years been used in traditional Chinese medicine remedies. Over the past few decades, artemisinin became popular for its efficacy in treating malaria victims; so-called artemisinin-based combination therapy currently stands as a stalwart solution for malaria sufferers.

But the availability of artemisinin has been uneven due to a theory that became ingrained in the scientific literature nearly 25 years ago: the conclusion that artemisinin can only be produced in the glandular trichome (GT) of the herb – that is, in the specialized hairs that grow on the outermost layer of the plant leaf.

De-Yu Xie, an NC State professor of plant and microbial biology, and graduate student Rika Judd study the sweet wormwood herb. Xie had for years been skeptical of the conclusion that artemisinin production was limited to GT cells – in other words, that GT was required for artemisinin production – and Judd sought proof of his hypothesis.

So Xie, Judd and collaborators in NC State's chemistry and plant and microbial biology departments used a number of techniques – genetic, gene expression, metabolomics and microscopy – to show that non-GT cells in both self-pollinated gland-bearing and glandless mutant A. annua plants have the capacity to produce artemisinin. The findings appear in *Molecular Plant*.

"Non-GT cells are more important than GT cells to provide a sufficient amount of artemisinin because the GT yield in the plant is generally very low; GT is about 2 to 3% of the dry weight of the plant," Xie said.

"We want to try to increase artemisinin content, and now we can try to do that through non-GT cells," Judd, the paper's first author, said. "We want to find a technique in which we can see what particular cells make artemisinin in addition to GT cells – and target those cells. Hopefully this finding will help our lab and other researchers develop new technologies to supply the high demand for anti-malaria drugs."

"I hope this paper will reshape research methodologies, hypotheses and practical applications on artemisinin in the future, so we can help billions of people who live in malarial risk areas," Xie said. "That means using new

technologies to produce 100 or more metric tons of artemisinin per year and at a lower price."

More information: Rika Judd et al. Artemisinin biosynthesis in non-glandular trichome cells of Artemisia annua, *Molecular Plant* (2019). DOI: 10.1016/j.molp.2019.02.011

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