Tobacco plants engineered to manufacture high yields of malaria drug

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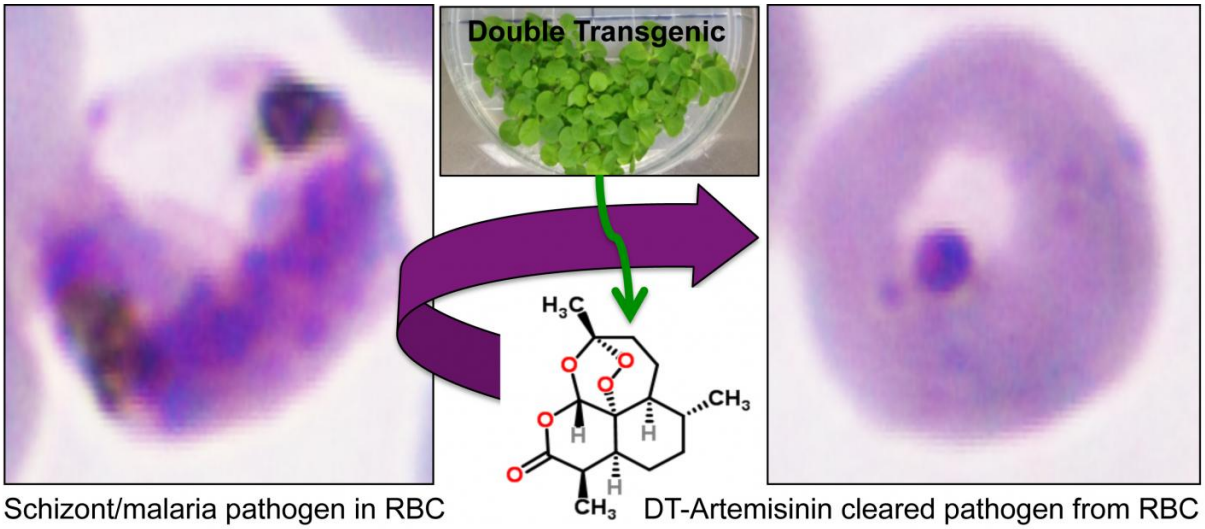

This photograph depicts the engineering of malaria drug artemisinin into a tobacco plant. Credit: Malhotra et al.

In 2015, the Nobel Prize in Physiology or Medicine was awarded in part for the discovery of artemisinin, a plant-derived compound that's proven to be a lifesaver in treating malaria. Yet many people who need the drug are not able to access it, in part because it's difficult to grow the plant that is the compound's source. Now, research has shown that tobacco plants can be engineered to manufacture the drug at therapeutic levels. The study appears October 20 in *Molecular Plant*.

"Artemisinin treats malaria faster than any other drug. It can clear the pathogen from the bloodstream within 48 hours," says senior author Shashi Kumar, of the International Centre for Genetic Engineering and Biotechnology in New Delhi, India. "Our research is focused on finding a way to make this drug available to more people."

Malaria infects more than 200 million people every year, according to the World Health Organization, and kills more than 400,000, mostly in Africa and Southeast Asia. The majority of those who live in malaria-stricken areas cannot afford to buy artemisinin. The drug's high cost is due to the extraction process and largely to the fact that it's difficult to grow Artemisia annua (sweet wormword), the plant that is the original source of the drug, in climates where malaria is common, such as in India. Advances in synthetic biology have made it possible to produce the drug in yeast, but the manufacturing process is difficult to scale up.

Earlier studies looked at growing the compound in tobacco—a plant that's relatively easy to genetically manipulate and that grows well in areas where malaria is endemic. But yields of artemisinin from those plants were low.

In the current paper, Kumar's team reports using a dual-transformation approach to boost the production of artemisinin in the tobacco plants: they first generated plants that contained transgenic chloroplasts, and the same plants were then manipulated again to insert genes into the nuclear genome as well. "We rationalized the expression of biosynthetic pathway's gene in different compartment that enabled us to reach the maximum yield from the double transgenic plants," he says.

Extract from the plants was shown to stop the growth progression of pathogen-infected red blood cells in vitro. Whole cells from the plant were also fed to mice infected with Plasmodium berghei, one of the microbes that causes malaria. The plant product greatly reduced the level

of the parasite in the blood. In fact, the researchers found, the whole plant material was more effective in attacking the parasite than pure artemisinin, likely because encapsulation inside the plant cells protected the compound from degradation by digestive enzymes.

But Kumar and his colleagues acknowledge that convincing people to eat tobacco plants is likely to be a hard sell. For that reason, he is collaborating with Henry Daniell, a professor of biochemistry at the University of Pennsylvania and one of the study's coauthors, with a plan to genetically engineer lettuce plants for producing artemisinin. The lettuce containing the drug can then be freeze dried, ground into a powder, and put into capsules for cost-effective delivery.

"Plant and animal science are increasingly coming together," Kumar says. "In the near future, you will see more drugs produced inside plants will be commercialized to reduce the drug cost."

More information: *Molecular Plant*, Malhotra et al: "Compartmentalized metabolic engineering for artemisinin biosynthesis and effective malaria treatment by oral delivery of plant cells." www.cell.com/molecular-plant/f … 1674-2052(16)30222-2 , DOI: 10.1016/j.molp.2016.09.013

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