

Engineered Chinese shrub produces high levels of antimalarial compound

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Growing *A. annua* plants. Credit: Ying Liu, Shanghai Xinhua News Agency

Artemisinin is a potent antimalarial compound produced naturally by the Chinese shrub *Artemisia annua*, commonly known as sweet wormwood. Currently, however, the low amount of artemisinin produced in the leaves of this plant does not meet the global demand. In a study published by April 24 in the journal *Molecular Plant*, researchers in China report a high-quality draft genome sequence of *A. annua* and their use of this information along with gene expression data to metabolically engineer plant lines that produce high levels of artemisinin. World Malaria Day is observed on April 25.

"Nearly half of the world's population is at risk of malaria," says senior study author Kexuan Tang of Shanghai Jiao Tong University. "Our strategy for the large-scale production of artemisinin will meet the increasing demand for this medicinal compound and help address this global health problem."

According to the World Health Organization, malaria affected approximately 216 million people in 91 countries in 2016 and caused an estimated 445,000 deaths worldwide that year alone. *Plasmodium falciparum* is the most prevalent malaria parasite on the African continent, and it is responsible for most malaria-related deaths globally. The best available treatment for malaria, particularly for cases caused by *P. falciparum*, is artemisinin-based combination therapy. In addition to its antimalarial activity, therapeutic effects of artemisinin have been reported for cancer, tuberculosis, and diabetes. However, the supply of artemisinin is limited because this medicinal compound typically makes up only 0.1%-1.0% of the dry weight of *A. annua* leaves.

To fully harness this compound's therapeutic potential, researchers have developed metabolic engineering strategies aimed at enhancing the expression of artemisinin biosynthetic pathway genes. These efforts failed to generate *A. annua* lines that produced high levels of artemisinin, though, primarily because they focused on modifying [gene expression](#) only upstream or downstream of the artemisinin biosynthetic pathway. A major hurdle for metabolic engineering strategies has been the lack of reference [genome](#) sequences and limited information about the genes involved in regulating artemisinin biosynthesis.



Kexuan Tang's research team and their *A. annua* plants.
Credit: Ying Liu, Shanghai Xinhua News Agency

To address this problem, Tang and his collaborators generated a high-quality draft assembly of the 1.74 gigabase *A. annua* genome, which contains 63,226 protein-coding genes, one of the largest numbers among sequenced plant species. It took several years to complete the genome sequence due to its large size and high complexity. The study adds a wealth of information about Asteraceae, one of the largest families of plants consisting of more than 23,600 species of herbs, shrubs, and trees distributed throughout the world, including many with considerable medicinal, ornamental, and economic importance.

"A major impediment to the exploitation of the Asteraceae resources in basic and breeding sciences has been the absence of reference genome sequences; to date, only the sunflower and chrysanthemum genomes have been released," Tang says. "The *A. annua* genome and transcriptome data we provide here will be a valuable asset for fundamental biological research on plant evolution and other topics as well as applied breeding programs."

Of particular importance, the *A. annua* genome sequence provided new insights into the entire metabolic pathway involved in artemisinin biosynthesis. Analysis of the protein-coding genes and gene expression patterns revealed the sophisticated regulatory networks underlying

artemisinin biosynthesis. Based on the genomic and transcriptomic data, the researchers identified novel genes involved in regulating artemisinin biosynthesis. By simultaneously increasing the activity of three [genes](#)—HMGR, FPS, and DBR2—spanning the entire artemisinin biosynthetic pathway, the researchers generated *A. annua* lines that produced high artemisinin levels—3.2% of the dry weight of the leaves.

Leveraging these findings, Tang and his team have sent artemisinin-rich seed samples to Madagascar, the African country that grows the most *A. annua*, for a field trial. They are also continuing to explore ways to enhance artemisinin production, with the goal of developing *A. annua* lines whose leaves contain 5% artemisinin.

"We hope our research can enhance the global supply of artemisinin and lower the price from the plant source," Tang says. "It is not expensive to generate high-level artemisinin lines. We have propagated hundreds of high artemisinin producer lines via cutting and selection, and scaled up the production of these [plants](#). Hopefully our high [artemisinin](#) transgenic lines will be grown at a massive scale next year."

More information: *Molecular Plant*, Shen, Q., Zhang, L., and Liao, Z., et al.: "The genome of *Artemisia annua* provides in 1 sight into the evolution of Asteraceae family and artemisinin biosynthesis" [DOI: 10.1016/j.molp.2018.03.015](https://doi.org/10.1016/j.molp.2018.03.015)

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