

ARTEMISININ

PRODUCT: Artemisinin, the key ingredient in the world's most effective anti-malarial drug, is extracted from *Artemisia annua*, commonly known as sweet wormwood. Today the pharmaceutical industry sources natural artemisinin from thousands of small farmers in Asia and Africa.

STATUS: Synthetic biologists at California-based Amyris, Inc. have inserted an engineered metabolic pathway in microbes to produce artemisinic acid, a precursor to artemisinin production. Pharmaceutical giant Sanofi-aventis is now attempting to scale up production of artemisinic acid in commercial fermentation tanks.

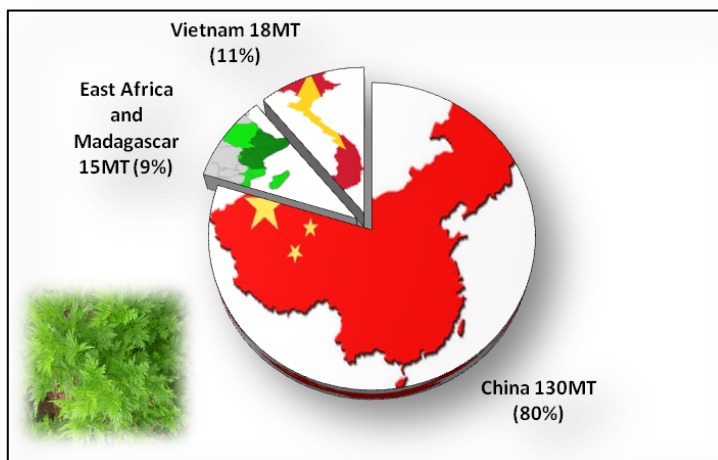



Figure 1: A2S2 Supply Forecast for 2011, by Region
<http://www.a2s2.org/index.php?id=33>

AFFECTED COUNTRY/REGION: At the present time 80% of the *Artemisia*/artemisinin is produced in China, 15% in Vietnam and the remainder in Kenya, Tanzania, Uganda, Madagascar and a small amount in India. Trials of *Artemisia* are being grown in Zimbabwe, South Africa and Nigeria.¹

MARKET: In 2011, the average price of artemisinin was around US\$550/kg. The global market for the production and extraction of *Artemisia*/artemisinin was between \$82.5 million and \$93.5 million.²

PLANT-DERIVED PHARMACEUTICAL INGREDIENTS AND SYNTHETIC BIOLOGY A NEW AND EMERGING ISSUE FOR CBD

This case study illustrates developments in synthetic biology that could disrupt the livelihoods of thousands of small farmers who cultivate *Artemisia* for the plant's anti-malarial compounds. These developments impact the sustainable use of biodiversity and fair and equitable sharing of benefits from the genetic resources that produce natural plant products. If biosynthesis of artemisinin can be successfully scaled up, the pharmaceutical industry will source future supplies of artemisinin from a handful of microbial cell factories instead of farmers in Asia and Africa. Artemisinin is just one example of a raw material that may be affected; it is conservatively estimated that at least 50% of today's commercial pharmaceutical compounds are derived from plants, animals and microorganisms. Seven of the ten largest pharmaceutical companies are now partnering with synthetic biology companies to develop synthetic biology production routes for pharmaceuticals previously processed from botanical sources. *Artemisia* is just one of hundreds of economically important natural plant compounds whose production may be switched to synthetic biology production in a very short time frame. No inter-governmental body is addressing the potential impacts of synthetic biology on the conservation and use of biodiversity and on the livelihoods of those who depend on agricultural export commodities (including high-value flavors, fragrances, essential oils, etc). The Convention on Biological Diversity is the most appropriate forum to address this new and emerging issue.



COMMERCIALIZATION: Near term (2013). Trial batches could be available from drug manufacturer Sanofi by the end of 2012.

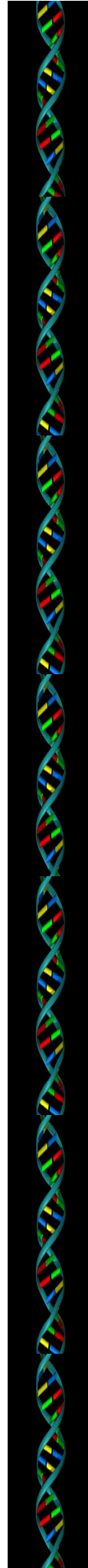
The key ingredient in the world's most effective drug treatment for malaria – artemisinin – is extracted from an ancient medicinal plant, *Artemisia annua*, commonly known as sweet wormwood. According to WHO, artemisinin-based combination therapies (ACTs) provide the most effective treatment against malaria. Today the pharmaceutical industry sources natural artemisinin from thousands of small farmers who grow *Artemisia annua*, primarily in China, Vietnam, Kenya, Tanzania, Uganda, Madagascar and India. The average crop area per farmer in China and Africa is around 0.2 hectares.³

However, the global supply of natural artemisinin has experienced boom and bust cycles and ACT drugs are priced out of reach for poor people. Because of the increased demand for artemisinin and the reinvigoration of anti-malaria campaigns, The Royal Tropical Institute of the Netherlands predicted in 2006 that *Artemisia* cultivation would grow to approximately 5000 smallholders and 500 larger-scale farmers.

CURRENT R&D: In 2006, Professor Jay Keasling of the University of California-Berkeley and 14 collaborators announced they had successfully engineered a yeast strain to produce artemisinic acid, a precursor to the production of artemisinin. Supported by a \$42.5 million grant from the Bill & Melinda Gates Foundation, the researchers achieved the complex feat of engineering the metabolic pathway, which comprised 12 new synthetic genetic parts.⁴ Inserted into yeast, the engineered pathway makes the yeast produce artemisinic acid, and a chemical process is then used to convert artemisinic acid to artemisinin. In 2008, Amyris granted a royalty-free license for its synthetic yeast to Sanofi-aventis for the manufacture and commercialization of artemisinin-based drugs, with a goal of market availability by 2013.⁵ According to the Assured Artemisinin Supply System (A2S2), trial batches could be available from Sanofi by the end of 2012.⁶ The companies assert that the new technology will diversify sources, increase supplies of high-quality artemisinin and lower the cost of ACTs.

If microbial production of synthetic artemisinin is commercially successful, pharmaceutical firms will benefit by replacing a diverse set of small suppliers with one or two production factories. The Royal Tropical Institute notes that, “pharmaceutical companies will accumulate control and power over the production process; *Artemisia* producers will lose a source of income; and local production, extraction and (possibly) manufacturing of ACT in regions where malaria is prevalent will shift to the main production sites of Western pharmaceutical companies.”⁷ The Royal Tropical Institute asserts that sufficient supplies of *Artemisia* could be met solely by increasing cultivation of wormwood.

The report estimates that between 17,000-27,000 hectares of *Artemisia annua* would be required to satisfy global demand for ACTs, which could be grown by farmers in suitable areas of the developing world. Indeed subsequent to the Royal Tropical Institute's report, farmers planted tens of thousands of additional hectares and in 2007 the artemisinin market became saturated with supply. Prices crashed from more than \$1,100 per kilogram to around \$200 per kilogram driving 80 processors and many small farmers out of business. As a result, availability once again dropped below demand.⁸ The 2007 production spike demonstrated the feasibility of meeting world demand for artemisinin with botanical supplies. The international drug-purchasing facility, UNITAID, subsequently established the Assured Artemisinin Supply System (A2S2) initiative to provide loans and supply chain investment to increase the *Artemisia* harvest to sustainable high levels.⁹ In 2011 artemisinin production from harvested crops was estimated at between 150-170 tonnes – close to 2007 levels. According to A2S2, “The present view is that artemisinin supply will be close to matching demand for 2012.”¹⁰



The Netherland's Tropical Institute's 2006 report warned that the prospect of synthetic artemisinin production could further destabilise a very young market for natural Artemisia, undermining the security of farmers just beginning to plant it for the first time: "Growing Artemisia plants is risky and will not be profitable for long because of the synthetic production that is expected to begin in the near future."¹¹

INTELLECTUAL PROPERTY RELATED TO BIOSYNTHESIS OF ARTEMISINIC ACID:

- US8101399: Artemisinic epoxide and methods for producing same. Assignee: The Regents of the Univ. of California. Published: 24 Jan 2012
- US7622282: Biosynthesis of isopentenyl pyrophosphate. Assignee: The Regents of the University of California. Published: 24 Nov 2009
- US7192751: Biosynthesis of amorpho-4,11-diene. Assignee: The Regents of the University of California. Published: 20 March 2007
- US7172886: Biosynthesis of isopentenyl pyrophosphate. Assignee: The Regents of the University of California. Published: 6 Feb 2007

FOR MORE INFORMATION

ETC Group has published several documents explaining and analyzing the impact of Synthetic Biology on biodiversity and livelihoods including *Extreme Genetic Engineering - An introduction to Synthetic Biology*, *The New Biomasters - Synthetic Biology and the Next Assault on Biodiversity and Livelihoods* and *The Principles for the Oversight of Synthetic Biology* available on our website http://www.etcgroup.org/en/issues/synthetic_biology

The Potential Impacts of Synthetic Biology on the Conservation & Sustainable Use of Biodiversity: A Submission to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical & Technological Advice (A Submission from Civil Society) <http://www.etcgroup.org/en/node/5291>

REFERENCES

¹ Personal communication with Malcolm Cutter, Director of FSC Development Services, UK and Project Manager of the MMV Artemisinin Programme, 24 April 2012.

² *Ibid.*

³ Assured Artemisinin Supply System (A2S2), *Production Cycle: from Artemisia to ACT*, 26 January 2012: <http://www.a2s2.org/index.php?id=50>.

⁴ Withers, S. T. and J. Keasling, "Biosynthesis and engineering of isoprenoid small molecules," *Appl. Microbiol Biotechnol.*, 73(5), pp. 980-90.

⁵ Details available on Amyris web site: <http://www.amyris.com>.

⁶ Assured Artemisinin Supply System (A2S2), A2S2 Newsletter No. 2, October 2011: <http://tinyurl.com/7fantux>.

⁷ Heemskerk, W. *et al.*, *The World of Artemisia in 44 Questions*, The Royal Tropical Institute of the Netherlands, March 2006.

⁸ Van Noorden, R., "Demand for Malaria drug soars," *Nature* 466, 3 Aug 2010, pp. 672-673.

⁹ <http://www.a2s2.org/>

¹⁰ A2S2, "Supporting Sustainable Artemisinin Supplies," Newsletter No. 1, July 2011.

¹¹ Heemskerk, W. *et al.*, *The World of Artemisia in 44 Questions*, The Royal Tropical Institute of the Netherlands, March 2006, p. i-ii: <http://tinyurl.com/7zoazkh>.