Artemisia - Artemisinin

A Case Study on Use of Synthetic Biology Replacements

Farmers affected: 100,000[1]

Volume: 200 Metric tonnes/year[2]

Market Value: Artemisinin: $76 million US Aretemisinin-based drugs: $340 million US[3]

Uses: Malaria Medication

Syn Bio Companies: Amyris

Hotspots: China (approx. 10,000ha); Vietnam. (approx. 1000ha); Madagascar

Also Grown In: India, Nigeria, Mozambique, Kenya, South Africa, Tanzania, Uganda, and Zimbabwe

Cultural importance: Use derived from 2000 years of Chinese herbalism

Biodiversity Considerations: Supplements income of small farmers, acts as a break crop

Quality Concerns: Artemisinin is a single compound. Excludes other important compounds. Although semi-synthetic artemisinin was approved by the World Health Organization, concerns were raised by chemists that WHO changed its standards to allow high levels of additional impurities in the syn bio derived version.[4]

Products: Artemisinin Combination Therapies (ACTs)

Feedstock: Sugar

Commercialization: On the market, sold by Sanofi Aventis

Overview

Artemisinin, the active ingredient from the Chinese herbal shrub *Artemisia annua*, or sweet wormwood, is the principal ingredient in a range of anti-malarial drugs authorized by the World Health Organization. By 2013, an estimated 100,000 small farmers in Asia and Africa were planting enough artemisia to meet world demand. Artemesia is grown primarily as a cash crop for sale to pharmaceutical companies.

Status: Syn bio artemisinin is already on the market

R&D Scale Up Commercialization

In April 2013 a "semi-synthetic artemisinin" (SSA) entered the market, produced via synthetic biology. This synthetic version was created by Amyris Biotechnologies in collaboration with Sanofi Aventis using $64 million dollars of philanthropic funds donated by the Bill & Melinda Gates Foundation.[5] It was initially supposed to replace a third to a half of global supply, although key researchers expressed their ambition to take over the entire global market. Suspiciously, the arrival of SSA coincided exactly with a crash in the price of naturally-derived artemisinin. Research suggests that many farmers have since stopped planting the crop in response to this price drop. Sanofi Aventis has shut down its syn bio factory for SSA- also because of the low price. The state of the future supply of this important anti-malarial compound is now unclear - and so are the livelihood implications for the farmers that grow it.

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For more information on Synthetic Biology please visit the ETC Group website:
www.etcgroup.org/synbio

What is Artemisinin?

Artemisia annua, or sweet wormwood, has been used by Chinese herbalists to treat malaria for over 2000 years. Since 1967, its active ingredient artemisinin has seen widespread use as the principal ingredient in a range of anti-malarial drugs authorized by the World Health Organization. These drugs are collectively known as Artemisinin Combination Therapies (ACTs), and are currently considered the most effective treatment against this very widespread and dangerous disease. Artemesia is also widely used in herbal tea form as a traditional protection against malaria and whole powdered versions of the leaf also appear to be effective.[6]

Artemisinin as a Natural product

Until as recently as 2013, natural artemisinin was sourced entirely from an estimated 100,000 small farmers in Asia and Africa, as well as wild harvesters of the crop in China.[7] Currently 80% of all artemisinin derived from artemisia crops is produced in China. Vietnam is a distant second (around 10%), with the remainder coming from Madagascar, Kenya, Tanzania and Uganda. A small amount is grown in India. Farmers have also been growing trial crops of Artemisia in Zimbabwe, South Africa and Nigeria. The average crop area per farmer in China and Africa is around 0.2 hectares.[8]

Cultural and Biodiversity Considerations

Artemesia is highly prized as a Chinese national treasure for its long history of use in curing malaria-like symptoms. Although difficult to grow in some areas, Artemesia has been widely adopted by tropical farmers, particularly in malarial regions of East Africa, where it can also be consumed as a herbal tea for medical benefits or transformed into other "whole plant therapies." Artemesia makes a good break or rotation crop for food crops such as rice and potatoes.

Synthetic Biology Production

The production of SSA, Semi-Synthetic Artemisinin, had been presented as a poster child for the field of Synthetic Biology, and is closely associated with Professor Jay Keasling - a serial biotech entrepreneur from the University of California at Berkeley. Artemisinin was chosen by Keasling and his start-up Amyris Biotechnologies as a demonstration molecule for proving out a synthetic biology process to develop isoprenoid chemicals (a class of 55,000 different molecules, many of them valuable). Artemisinin was interesting as a first candidate because its connection to a serious disease could attract philanthropic funds.[9] Supported by a $64-million grant from the Bill & Melinda Gates Foundation, the researchers engineered yeast to produce artemisinic acid (a precursor) and convert that to artemisinin.[10] Sanofi (Sanofi Aventis) announced in April 2013 that they had manufactured 35 metric tonnes (MT) in its first batch. It indicated plans to annually produce enough Semi-Synthetic Artemisinin (SSA) to meet between a third and a half the global demand.[11]

Although Sanofi's production was slated to increase to 60 MT per year, it appears that in reality Sanofi were unable to sell this first run of SSA to any ACT (Artemesia Combination Therapies) manufacturer because their price was above market cost; and in 2015 they produced no SSA at all. This was linked to a collapse in artemisinin prices. They have decided to sell the plant to their contractor, HuvePharma. HuvePharma told *Nature* magazine that they may switch back to botanically-derived artemisinin if they can't make the process cheaper.[12]

Implications and The Future

A 2006 report from the Netherlands-based Royal Tropical Institute had predicted the effects of introducing synthetic sources of artemisinin: "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."[13] Additionally, artemisinin experts warned against the human cost of disrupting the recently stabilized botanical market with a synthetic version. "If it's brought in too fast it could create huge shortages, because people will stop producing the natural stuff,"[14] said Malcolm Cutler, technical adviser to the A2S2 initiative.

That may indeed have been the initial impact of introducing SSA. Upon the arrival of the syn bio version, 2014 prices of botanical artemisinin dropped to a decade low; and subsequently plantings reportedly fell by two-thirds. The price fell so low that even SSA was overpriced and that's the reason Sanofi couldn't sell theirs. Farmers looked elsewhere for income. Far from calming market volatility, SSA may have helped fuel price volatility and undermined a valuable income source for tens of thousands of farmers.

Worryingly, Jay Keasling meanwhile has indicated that the team behind semisynthetic artemisinin hope to switch the entire global production of artemisinin away from botanical artemesia towards syn bio-derived artemisinin. At a conference in Cambridge on the eve of launching SSA commercially, Keasling said "There are moves afoot to replace the entire world supply with this source" adding "Early on, it was not about replacing the agricultural form. In part that was politics too. If I went out into the public and said we are going to replace this they might stop planting and now I think its nearly inevitable that it will shift over".[15] Switching entire global production to SSA would be a highly dangerous move. If there were to prove a problem with synthetic production, drugmakers would have lost the botanical supply for a needed medication.

Endnotes

1 Global estimate of 100,000 artemesia growers provided by Charles Giblain, CEO Bionexx, Madagascar. Personal communication Jun 17th 2013

2 Provided by Charles Giblain, CEO Bionexx, Madagascar. Personal communication Dec 18 2014.

3 Estimate based on average prices for artemisinin of $380kg – source Charles Giblain, Bionexx – see www.a2s2.org/upload/5.ArtemisininConferences/4.2014China/Day1/11.MadAfCountryReportGIBLAIN.pdf

4 Bhupinder P Kambay, Presentation to A2S2 conference Nairobi, Kenya "Proposed Changes to Specifications for Artemisinin as an API and Starter Material" 16th January 2013 – see www.a2s2.org/upload/5.Artemisinin Conferences/1.2013Kenya/Presentations/Day2/6.Proposed ChangesARTSpecificationsKamtech.pdf

5 Mark Peplow, "Synthetic biology's first malaria drug meets market resistance" *Nature News* 23 Feb 2016 - www.nature.com/news/synthetic-biology-s-first-malaria-drug-meets-market-resistance-1.19426

6 Janet Lathrop, "Whole Plant Therapy Shows Promise to Beat Malaria Parasites' Drug Resistance" Jan 5th 2015, UMass Amherst - www.umass.edu/newsoffice/article/whole-plant-therapy-shows-promise-beat

7 Global estimate of 100,000 artemisinin growers provided by Charles Giblain, CEO Bionexx, Madagascar. Personal communication Jun 17th 2013

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

9 In person Interview with Vincent Martin, former chief Scientist Amyris Biotechnologies – Montreal, Feb 2 2012

10 Mark Peplow, "Synthetic biology's first malaria drug meets market resistance" *Nature News* 23 Feb 2016 - www.nature.com/news/synthetic-biology-s-first-malaria-drug-meets-market-resistance-1.19426

11 Sanofi news release, "Sanofi and PATH announce the launch of large-scale production of semisynthetic artemisinin against malaria" April 11 2013 - www.path.org/news/press-room/422/

12 Mark Peplow, "Synthetic biology's first malaria drug meets market resistance" *Nature News* 23 Feb 2016 - www.nature.com/news/synthetic-biology-s-first-malaria-drug-meets-market-resistance-1.19426

13 Heemskerk, W. *et al., The World of Artemisia in 44 Questions,* The Royal Tropical Institute of the Netherlands, March 2006, p. i-ii: www.kit.nl/health/wpcontent/uploads/publications/879_The%20world%20of%20Artemisia%20in%2044%20questions.pdf

14 Mark Peplow, "Malaria drug made in yeast causes market ferment" *Nature News.* 13 February 2013 - www.nature.com/news/malaria-drug-made-in-yeast-causes-market-ferment-1.12417

15 Presentation by Jay Keasling at The Future of Nature conference, Cambridge UK April 2013. Partial transcripts provided in presentation by Charles Giblain, Bionexx – see www.a2s2.org/upload/5.ArtemisininConferences/4.2014China/Day1/11.MadAfCountryReportGIBLAIN.pdf