# STAR ANISE

**PRODUCT:** Shikimic acid is the key raw material for the manufacture of oseltamivir (Tamiflu), an anti-viral drug. Shikimic acid is traditionally sourced from star anise, the pod of the Chinese medicinal plant, *Illicium anisatum.*


**STATUS:** After the outbreak of bird flu in 2005 demand for Tamiflu soared because countries began stockpiling the drug. Because of a shortfall in supplies of botanically-derived star anise, synthetic biologists began engineering the metabolic pathway of bacteria to produce shikimic acid via fermentation.

**AFFECTED COUNTRY/REGION:** China produces about 80% to 90% of the world's star anise. Chinese farmers are heavily affected by fluctuating commodity prices and new synthetic technologies.

**MARKET:** In 2005, the price of Chinese shikimic acid derived from star anise soared to more than $400/kilogram, from $40/kg. Worldwide sales of the anti-viral drug fluctuate: in 2009 Tamiflu sales were $2.9 billion; in 2011 sales reached only $406 million.[1]

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

This case study illustrates how a key pharmaceutical ingredient, shikimic acid – traditionally derived from star anise cultivated by Chinese farmers – can be rapidly replaced by a new technological production process. Using synthetic biology, shikimic acid is now being produced commercially in drug industry fermentation tanks. The transition took less than a decade. Shikimic acid 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. 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 exports (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:** Most of the shikimic acid used by Roche, a Swiss pharmaceutical company, to manufacture Tamiflu is now sourced from microbial fermentation. Roche has contracts with Sanofi Aventis (France) and others to provide the shikimic acid produced in 'cell factories.'

The production of a major anti-viral drug, Tamiflu, depends on shikimic acid, which is traditionally sourced primarily from star anise, the star-shaped pod of the traditional Chinese medicinal plant, *Illicium anisatum.* Roughly 80-90 percent of the world's star anise is grown in southwestern China, primarily in Guangxi and Yunnan provinces. An estimated 66 percent of

China's star anise harvest is used to make Tamiflu.[2] (Star anise is also valued as a spice and for medicinal uses.) In Guangxi province alone, some 350,000 hectares of farmland are devoted to the star anise tree with an annual output of 80,000 tonnes.[3] After planting it takes around six years for star anise trees to bear fruit. The process of extracting and purifying shikimic acid from star anise seeds is expensive. It takes about 30 kg of star anise to yield 1 kg of shikimic acid, enough to treat one person.[4] With the heightened threat of global pandemics (bird flu in 2005 and swine flu in 2009) demand for Tamiflu soared and drug company Roche (maker of Tamiflu) couldn't meet demand due to a shortage of star anise. Because of the shortfall in botanically sourced shikimic acid, synthetic biologists and chemists increased efforts to develop alternative production routes in *e. coli*.[5]

**CURRENT R&D:** Michigan State University professor, John Frost, founded a small start-up company, Draths Corp., in 2005 to produce building blocks for the chemical, pharmaceutical, and food industries – including shikimic acid. Frost and his co-inventor, Karen Draths, patented a technology for making shikimic acid in engineered *e. coli* that was subsequently licensed to Roche.[6] Today the co-inventors hold a family of 14 patents and patent applications that cover methods and materials for the production of shikimic acid (see below). In November 2011, Draths Corp. and its intellectual property were acquired by synthetic biology company Amyris, Inc.[7]

By the end of 2005 Roche was reportedly producing about one-third of its shikimic acid supply from the microbial fermentation process.[8] According to Roche, "a specific strain of E. coli which, when overfed glucose, produces SA [shikimic acid]. During the process, the E. coli are fed, fermented, and broken down to extract the SA. Enormous vessels (each the size of 2 city buses) are required to accommodate the volume of E. coli mixture needed."[9]

Roche has continued to increase its fermentation capacity, suggesting that the microbial production of shikimic acid for Tamiflu production is competitive in price with shikimic acid derived from star anise. In March 2012 Roche told ETC Group, "For our Tamiflu production we mostly rely on the microbial fermentation process."[10] The company would not specify the quantity or percentage of shikimic acid derived from microbial production.

## INTELLECTUAL PROPERTY RELATED TO BIOSYNTHESIS OF SHIKIMIC ACID:

[Note: Frost and his co-inventor hold a family of 14 patents and patent applications. These include the first two listed below, for example.]

- US8080397: Biocatalystic synthesis of quinic acid and conversion to hydroquinone by recombinant microbes. Assignee: Board of Trustees Michigan State University. 20 Dec 2011
- US7790431. Methods and materials for the production of shikimic acid. Assignee: Board of Trustees Michigan State University. Published: 7 Sept 2010
- US20120052547A1: Methods for control of flux in metabolic pathways through protease manipulation, No Assignee. Published: 1 March 2012.
- US20110008867A1: Compositions and methods for the production of a compound. Assignee: GreenLight Biosciences. Published: 13 Jan 2011.

## 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 Biomassters - 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

## REFERENCES

[1] www.evaluatepharma.com
[2] Zhuang Pinghui, "Drought hit harvest of star anise, vital to flu fight," *South China Morning Post* online, March 29, 2010.
[3] Zhuang Pinghui, "Drought hit harvest of star anise, vital to flu fight," *South China Morning Post* online, March 29, 2010.
[4] Andrew Pollack, Is Bird Flu Drug Really So Vexing? Debating the Difficulty of Tamiflu, *New York Times*, November 5, 2005.
[5] Saptarshi Ghosh, Yusuf Chisti, Uttam C. Banerjee. In press 2012. Production of shikimic acid, *Biotechnology Advances*, online 13 March 2012. http://dx.doi.org/10.1016/j.biotechadv.2012.03.001
[6] Andrew Pollack, Is Bird Flu Drug Really So Vexing? Debating the Difficulty of Tamiflu, *New York Times*, November 5, 2005. We do not know if Roche is currently using the proprietary fermentation method developed by Frost or an alternative method.
[7] Anonymous, "Amyris Acquires Draths," *Chemical Week*, 4 Nov 2011.
[8] David Bradley, Star role for bacteria in controlling flu pandemic? Nature Reviews Drug Discovery 4, 945-946 (December 2005) | doi:10.1038/nrd1917
[9] The Challenges of Tamiflu Manufacture, available at: www.roche.com/med_mb091105jvk.pdf
[10] Email communication from Claudia Schmitt, Roche, March 21, 2012.