Synthetic Biology, Biodiversity & Farmers

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Case studies exploring the impact of synthetic biology on natural products, livelihoods and sustainable use of biodiversity

Synthetic Biology, Biodiversity and Farmers

ETC Group

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Introduction

A fundamental shift is underway in how food, flavor, cosmetic and fragrance ingredients are being produced for global markets. The new game in town is ***biosynthesis*** – the artificial production of key compounds by synthetically engineered organisms. While consumers, farmers and the natural world have already had to grapple with the impacts of the last synthetic revolution (synthetic chemistry), which has created many toxic, harmful or noxious substances and polluted systems, this next synthetic revolution (synthetic biology) is set to have equally disruptive effects. These impacts range from safety and environmental concerns to very profound social and economic upturning of livelihoods and landscapes.

At the sharpest end of this disruption are the farmers, growers, pickers and harvesters, particularly in the tropics, who provide the natural products that make up the ingredients in our foods, cosmetics, soaps, textiles and more. Consumers and workers will also be affected.

In this report ETC Group presents a series of case studies outlining ways that specific products are being bio-synthetically created, and how current livelihoods from traditional agricultural production may be adversely affected as these synthetic biology-based substitutes for high value commodities enter the market. Several of these synthetic substitutes are already in commercial use; some taking major market share already; and many more are rapidly headed towards commercialization, potentially displacing the work of already marginalized peoples in their wake.

What is Synthetic Biology?

Synthetic biology, dubbed "genetic engineering on steroids," broadly refers to the use of computer-assisted, biological engineering to design and construct absolutely novel synthetic biological segments, devices and systems that do not and never have existed in nature; it also refers to the redesign of existing biological organisms using these techniques. Synthetic biology attempts to bring a predictive engineering approach to biological genetic engineering using genetic "parts" that are thought to be well characterized and whose behavior can in theory be rationally predicted.

> ***"The overall aim of synthetic biology is to simplify biological engineering by applying engineering principles and designs—which emanate from electronic and computer engineering—to biology."*** [1]

With synthetic biology, the goal is to produce high-value flavor/fragrances by using engineered microbes instead of relying on costly botanical imports or conventional chemical synthesis. The biosynthetic manufacturing platform involves the engineering of genetic pathways in microorganisms, which alters them so they produce molecular compounds that previously have been extracted from plants. Scientists and software engineers are tweaking the DNA of existing microorganisms as well as designing new ones from scratch.

In the words of one industry analyst: "There is potential for biosynthetic routes to completely replace any natural sources." – Kalib Kersh, Lux Research, quoted in Chemical & Engineering News.[3]

The Switch to Ingredient Markets

Over the past decade, before world oil prices plunged, fledgling syn bio start-ups (with the financial backing of fossil fuel corporations) made grandiose claims about using designer microbes to produce plentiful, low-cost biofuels in giant fermentation tanks. Manufacturing petrochemical substitutes at commercial scales proved elusive, however. Now with energy markets sputtering, most syn bio companies are giving up on biofuels and turning to high-cost, low volume flavor and fragrance molecules that can be economically produced in smaller batches.[2]

Biodiversity – especially exotic plants and animals – has been the source of natural flavors and fragrances for millennia. Plants, animals and microorganisms are prolific generators of bioactive flavor/fragrance compounds, known as secondary metabolites, that, once extracted, are widely used in food, feed, cosmetics, chemicals and pharmaceuticals.

The world's largest flavor and fragrance corporations are eager to partner with synthetic biology companies because of increasing production uncertainties caused by climate change, as well as the alluring potential of securing cheaper, uniform and more accessible sources of economically desirable natural ingredients.

Metabolic Pathways to Everything

Even though plant product metabolism is extremely complex, with advances in molecular biology and engineering, researchers are attempting to pinpoint the precise biochemical instructions in the cells of a living organism that result in the production of bioactive molecular compounds. In one well-studied plant, *Arabidopsis thaliana* (a.k.a. mouse-ear cress or thale cress), at least 20% of the genes are thought to play a role in the biosynthesis of secondary metabolites.[4] The complex interaction of genes and enzymes in their natural context all play a role in the plant's "metabolic pathway" – the means by which it produces a useful chemical compound.

Using "metabolic pathway engineering," synthetic biologists are turning microbial cells into "living chemical factories" that can be *induced to manufacture substances they could never produce naturally*. To date, synthetic biology firms are honing in on the best-known metabolic pathways such as terpenoids, polyketides, alkaloids – these pathways are the keys to producing tens of thousands of natural product families at the molecular level.

"There is potential for biosynthetic routes to completely replace any natural sources."

Kalib Kersh, Lux Research, quoted in Chemical & Engineering News.[3]

To scale up the production of a desired compound, the novel biosynthetic pathway (constructed with synthetic DNA) is inserted into a microbial host (yeast, bacteria, fungi or algae strains, for example) that feed on plant sugars in giant (e.g., 200,000-litre) fermentation tanks. In the words of synthetic biologist Jay Keasling: "We ought to be able to make any compound produced by a plant inside a microbe."[5]

The engineering of microbes for industrial purposes is nothing new, but synthetic biology start-ups are accelerating the process with computer engineering principles and highly automated, robotic systems. In a mostly random process, software-directed robotic systems design, build, test and analyze DNA sequences and active compounds to identify promising candidates and optimize biomolecular pathways in microbes. Despite the staggering complexity of biological systems, synthetic biologists compare themselves to industrial product designers: "This design strategy can be likened to building millions of variants of a chemical factory, selecting or screening for control system variants that yield the most product and discarding all but one or two of the most productive designs."[6] One synthetic biology company refers to its employees as "organism designers" who work in a "foundry," not at a lab bench.[7]

In the words of one venture capitalist, Bryan Johnson, founder of the OS Fund, the ultimate goal of syn bio is to control biology and make it predictable: "We aren't there yet with biology... I can't just sit down and program biological code to create a particular outcome on a more complex scale. What's standing between us making good use of that is our ability to make it predictable."[8]

Despite the techno-rhetoric, the design and control of synthetic organisms is far from routine, simple or inexpensive. Biosynthetic pathway engineering is highly complex. Just two examples:

- **Researchers at Amyris, Inc.** (California) successfully engineered the metabolic pathway of yeast to produce artemisinic acid, a precursor of artemisinin, an effective drug to treat malaria, which is typically sourced from the Chinese wormwood plant.[9] The biological engineering involved at least 12 new synthetic genetic parts[10] (and more than $53 million in research grants[11]).
- **Evolva** (Switzerland) commercialized a proprietary yeast biosynthesis platform for the production of vanillin – a key flavour compound in natural vanilla. In 2009 researchers disclosed that construction of the *de novo* pathway in yeast incorporates bacterial, mold, plant and human genes.[12]

Both products are now commercially available and intended for human ingestion.

Industry's Synbio Advantage

For the industrial flavor / fragrance industry, the synthetic biology platform could offer two major advantages:

1) **The potential to secure more uniform, uninterrupted supplies of high-value raw materials in factory-based fermentation tanks.** In other words, companies would be unencumbered by climate, weather, crop failure, price and political volatility or the logistical complexity of sourcing raw materials from farmers and other suppliers in remote locations.

2) **The ability, under current regulations in the USA and Europe, to market biosynthesized flavors and aroma compounds as "natural" products.**[13] In other words, biosynthetic products manufactured via microbial fermentation are deemed "natural" or "substantially equivalent" to a botanically-derived product. In contrast, chemically synthesized flavors/fragrances derived from petroleum cannot be labeled "natural."[14] Research shows that consumers have a strong preference for the "natural" label – despite the murkiness that surrounds it. One survey indicates that almost 60% of consumers in the United States look for the word "natural" when they shop for food products.[15] Because regulations governing "natural" products specifically permit "fermentation" and "microbiological" processes, the biosynthesis of flavor/fragrances in engineered microbes is not only positioned to compete with natural, botanically derived counterparts – they will also have an advantage over synthetically derived flavors/fragrances.[16] The bottom line: consumers will have no way of knowing if a "natural" flavoring or scent is derived from industrial, genetically engineered microbes or from a traditional botanical source.

Answering the Hard Questions on Synthetic Biology

Do synthetic biology-derived ingredients pose a threat to human health or the environment?

Synthetic biology techniques are more powerful than previous genetic engineering techniques, but threats will depend on each specific application. There is little or no data on long-term impacts (including health risks) from various applications of these techniques, as well as *no* regulations. Synthetic biology organisms may produce novel contaminants and could have significant implications for ecosystems if they are released or escape into an ecosystem and continue to multiply.

There are also overall impacts on farmers, land use and concerns about the consolidation of corporate power over so many commodities.

If the production is contained in vats, are there safety risks?

There is insufficient understanding about synthetic biology techniques or about how to contain the engineered organisms. Although some production of synthetic biology organisms (algae and yeast) is done in factory fermentation vats, organisms and viruses even from high containment laboratories routinely escape through human error. Commercial synthetic biology facilities are not necessarily containment facilities, and synthetic biology facilities have already experienced spills and escapes of synthetic biology organisms. These organisms are alive and can evolve, recombine, or change.

Is synthetic biology more "sustainable" because it's "natural" and "bio-based"?

Several synthetic biology companies are misleadingly marketing their ingredients as "sustainable," "natural" and "bio-based." For example, although the synthetic biology-engineered organisms carry out fermentation, a natural process, the organisms themselves are highly unnatural and synthetically constructed.

Photo above: Polinating vanilla flowers by hand - (cc) Brocktopia

The term "bio-based" refers to the sugars – including cellulose – that synthetic organisms consume. However, bio-based does not always mean "sustainable" or ecologically responsible. Debates over biofuels and bioenergy have shown that the chemical and water-intensive agriculture used to grow the plant sugars (such as sugar cane or GMO corn) are not sustainable. In addition to their significant ecological impacts from chemical contamination, these feedstock industries are associated with destructive forestry operations, land grabs and land clearances.

Some synthetic biology companies claim that the ingredient synthesized replaces one that would have been unsustainably extracted from the wild – e.g. palm oil. However, these claims are questionable and do not consider existing alternatives; they need to be carefully scrutinized.

If the synthetic biology-derived ingredient is "nature-identical" to the botanical version, what are the concerns?

Most of the synthetic biology-derived ingredients currently being produced are for single flavor, fragrance and cosmetic compounds such as vanillin (vanilla flavor), nootkatone (grapefruit flavor) or squalane (moisturizing oil). Natural products will usually have a much more complex array of compounds and so the quality is quite different. Synthetic biology companies argue that the final compound produced is "nature-identical" (chemically similar) to the naturally-derived version and therefore does not need any additional assessment. However, the synthetic biology processes themselves may create unexpected contaminants, toxins or allergens that may be hard to control for. In addition, the process of replacing natural commodities with unnatural ones raises significant environmental dangers, and concerns about the impacts on small farmers' livelihoods, cultures, and national economies, as shown in these case studies.

Photo above: Consumer demand shapes industry - (cc) Hazel Isles

Disrupting Who?

Putting Synthetic Biology Developments in Historic Perspective: Technology, Livelihoods and Commodity Trade In Botanical Product

History shows that the introduction of new technologies can have profound and devastating impacts on the livelihoods of farmers, agricultural workers and national economies. In the colonial era, for example, European expansion accelerated the flow of food plants and livestock from their colonies, and Europeans began to largely control the flow of crops and to monopolize production and processing technologies important to commercialization (e.g., cotton, rubber, coffee, tea and spices). These technology transfers created patterns of long-lasting economic dependence and poverty in the colonized countries.

Developments in chemistry toward the end of the 19th century – particularly in Germany, France and the United Kingdom – propelled a new technology wave that reduced and/or eliminated the demand for a wide array of raw materials once sourced in the global South. Chemically-synthesized dyes from Germany, for example, quickly replaced natural dyes such as the madder root. By 1900 Turkey's natural dye market disappeared, due to a chemically synthesized substitute. When blue synthetic dyes went into large-scale production in Germany in 1897, Indian farmers were cultivating 574,000 hectares of indigo from a variety of plants. In the 1930s, the plastics 'revolution' destroyed many other natural industries as well as creating vast pollution. Then, following World War II, similar market disruptions followed the introduction of synthetic petroleumbased fibers.

Continued overleaf...

The first beneficiaries of sudden technology shifts have historically been those who develop and/or control the new technology. The "losers" are the producers of primary commodities who were unaware of the imminent changes or who could not make rapid adjustments in the face of new demands and technologies.

In order to assuage concerns that synthetic biology could result in the same win/lose scenario, some advocates have argued that the transfer of field production to vat production could benefit local ecosystems and local food security. Amyris, Inc. in Berkeley, CA has suggested that the elimination of the field production of the Chinese wormwood shrub for a pharmaceutical compound (artemisinin) could allow farmers to grow more potatoes.

In fact, this is not economically or ecologically plausible; many of these plants grow in difficult environments not suited for other crops. Farmers not only benefit substantially from wormwood shrub production, but also the antimalarial tea they brew at home is directly beneficial to their families and communities. Potatoes, on the other hand, are notoriously destructive to soils, and farmers are often obliged to make extensive use of crop chemicals with all the attendant economic, health and environmental damages.

In another case, undercutting natural vanilla production in Madagascar (and its replacement with vat production in Switzerland) would immediately damage the livelihoods of family producers and oblige them to cut back the wonderfully diverse and valuable forests that they need to create the conditions necessary for their vanilla plants.

Theoretically speaking, however, synthetic biology could stimulate demand for more of a given natural product. The development of synthetic rubber in the USA during World War II and after led, within a couple of decades, to synthetic rubber occupying more than 60% of the global market. At the same time, post-World War II affluence and the demand for tires also increased the demand for natural rubber and the producer countries in Southeast Asia have benefited. Likewise, the discovery of a bacterium in Thailand in the 1950s, that led to the introduction of high fructose corn syrup (HFCS), could have been expected to wipe out demand for sugar cane and sugar beet. In reality, the explosion in consumer demand for sweeteners – and cars for ethanol – meant that the demand for both corn and sugarcane boomed, for better or worse. Many scenarios have to be considered in each case. Might this be so for natural flavors and fragrances? 95% of the market has already been lost to chemical synthetics. The remaining 5% still sustains tens of millions of farm families around the world. These natural flavors and fragrances are typically richer and more complex than factory-made versions, and in the past few years major food processors and even fast food companies (including Pizza Hut and Taco Bell) are going back to natural flavors in the face of widespread consumer disaffection. This is a battle that can be won.

Schumpeter's dictum on "creative destruction" still dominates, however. Not just change – but also the threat of change – can be highly destructive, even if it may turn out to be beneficial in the long run. Simply the possibility that a crop could be grown in a vat can disrupt supply chains and damage producer prices, causing farmers to abandon their best opportunities for fear that there will be no one to sell to at harvest time, something which already impacted the supply of artemisium, a valuable medicine. If the competition is frightened into retreat, synthetic biology doesn't have to be technologically successful to be commercially successful. The bottom line is that industrial "creative destruction" is always devastating to marginalized peoples. These long-term changes shouldn't be considered before those affected are able to be full participants in the political and economic negotiations involved in any technological change.

The Global Flavor & Fragrance Industry

In 2013 the global flavor and fragrance market was valued at $23.9 billion[17] and is expected to grow to over $35 billion by 2019.[18] This figure reflects the value of ingredients for processed foods and fragrances only, and does not include the value of crops like coffee and cacao beans, which are also commonly used to flavor processed foods. The industry is increasingly concentrated in the hands of four multinational firms[19] which controlled 58% of the market in 2013 – Givaudan, Firmenich, IFF and Symrise.[20] The top 10 companies collectively accounted for an estimated 80% of total industry sales.[21] At least six of these companies have R&D agreements with synthetic biology firms.[22]

F&F giants are pursuing every feasible route to secure cheaper and more accessible raw ingredients – both natural (sourced from their natural environment) and synthetic (chemicals synthesized from petroleum). Although the flavor and aroma industry likes to emphasize the use of "natural" ingredients, the vast majority of flavors and fragrances are the product of chemical synthesis: an estimated 95% of the compounds used in fragrances are synthesized from petroleum – not sourced from plants, animals or microorganisms.[23] Even so, the main F&F firms still buy thousands of plant and animal-derived ingredients from dozens of countries.

Flavors and fragrances are essential ingredients in the manufacture of household cleaning products, perfumes, cosmetics, pharmaceuticals, food & beverages, aromatherapy and more. For example, the soft drink industry is the major consumer of natural flavors/fragrances, especially essential oils of citrus origin.[24] In fact, "cola" soft drinks cannot be produced without essential oils like lemon or lime.[25] The F&F industry currently sources 200 to 250 different botanical crops grown on an estimated 250,000 hectares worldwide. Around 95% of these crops are grown by small-scale farmers and agricultural works, mostly in the global South.[26]

An estimated 20 million small-scale farmers and agricultural workers depend on botanical crops grown for natural flavors and fragrances.[27] (This is a low estimate.) Flavor & fragrance industry trade groups do acknowledge that these botanicals are "highly important in terms of their socio-economic impact on rural populations and may also have important environmental benefits within agricultural systems."[28]

From ETC Group's research it is clear that the very largest players in the Flavor and Fragrance industry are now investing significant sums in synthetic biology production of key compounds. These are players who routinely source thousands of raw materials from tens of millions of farmers and pickers to transform their products into tens of thousands of consumer ingredients.

Those enthusiastically embracing synthetic biosynthesis include DSM, BASF, Givaudian, Firmenich, International Flavors and Fragrances and Robertet. The syn bio ingredients they are switching to range from fragrances such as patchouli, rose oil and ambergris to cosmetic compounds such as squalane and shea butter to food ingredients such as vanillin, stevia and saffron.

Sourcing raw materials from a high tech vat rather than from millions of diverse farmers offers them simpler supply chains and increases corporate control over the production process. This current ongoing switch to syn bio derived-ingredients, which does little to benefit the consumer or the farmer, makes sense only in light of the economic interests of these large and powerful ingredients brokers.

Endnotes to the Introduction

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Agarwood Oil

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: Difficult to estimate

Market Value: $6-12 Billion US[1]

Volume: 4,870 litres/year

Uses: Perfume and Cosmetics

Syn bio Companies: Evolva, Efflorus

Hotspots: India, Indonesia, Malaysia, Vietnam, Cambodia, Thailand, Laos, Papua New Guinea

Also Grown In: Bangladesh, Bhutan, Brunei, Darussalam, China, Myanmar, Singapore and Sri Lanka,

Cultural Importance: Cultural and religious significance in ancient civilizations around the world - mentioned extensively in some of the world's oldest written texts

Biodiversity Considerations: Collection in the wild is endangering *Aquilaria* species (tree), but new intercropped plantations claim to use agroecological practices that benefit biodiversity.

Quality Concerns: Natural agarwood oils have many chemical constituents. Syn Bio Companies usually manufacture only one component of the natural product, not all the molecules present in the natural product.

Method: Yeast

Commercialization: Efflorus' product may be on the market by 2017.

Overview

Agarwood oil or Oud, a fragrant oil found in the damaged heartwood of Southeast Asian *Aquilaria* trees, has a long and sacred history as an important fragrance used for thousands of years in the religious and cultural ceremonies of ancient civilizations. Unfortunately, the wild collection of this expensive oil is endangering the *Aquilaria* species and so trade in wild agarwood is now illegal. In response, *Aquilaria* plantations are being established to farm agarwood on a more agroecological basis. Two biotech companies (Evolva and Efflorus) have made it known that they are working on producing the main components of agarwood through synthetic biology. At this point neither has a timeline for commercialization, methodology or product names.

Status: Syn bio agarwood may be available in 2017

R&D — Scale Up — Commercialization

What is Agarwood Oil?

Agarwood (also known as Gaharu or Oud oil) is the fragrant resinous heartwood found in trees from the genus *Aquilaria* (Thymelaeaceae), native to southeast Asia.[2] This highly-prized but endangered aromatic, resinous wood is only formed inside the tree if it becomes damaged or diseased due to cutting, pest or insect disturbance, microbial infection, fire, etc.[3] Agarwood is used to make essential oils for perfumes, and for wood chips to make incense. It is described as "...a high-demand ingredient in fine perfumery due to its warm, unique balsamic notes with sandalwood–ambergris tonalities."[4]

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

Agarwood as a Natural Product

Agarwood trees traditionally grow throughout South and Southeast Asia,[5] but Malaysia is the major producer of high-quality agarwood.[6] It is not known how many people earn their livelihoods from collecting and processing agarwood – especially because most of the trade is illegal. Foreign nationals as well as locals are reportedly involved in illegal agarwood harvesting in Malaysia.[7]

According to industry sources, the estimated value of the global trade in agarwood is a staggering $6 to $12 billion US.[8] Official figures are not available from any country because most of the trade is black market.[9] High-quality agarwood essential oil – priced wholesale at $15,000 US per liter – has been dubbed "liquid gold." The retail value is often triple that amount.[10] The price of agarwood oil ranges from $100 US/kg for lower quality material up to $100,000 US/kg for superior, high-purity oil.[11] In 2012, global trade in agarwood essential oil was 4,870 litres.[12] Key importers of agarwood essential oil include Saudi Arabia, the United Arab Emirates, Bahrain, Malaysia, Singapore, China, Taiwan and Japan.[14] In 2013, global trade in agarwood chips and powder was 4.7 million kg – the price of agarwood chips ranges from $20 US to $6,000 US per kg; high quality wood sells for up to $30,000 US per kilogram.[13] Major importers include Singapore, China, Taiwan, Japan, Saudi Arabia and the United Arab Emirates.[14]

Will engineered microbes in fermentation tanks compete with newly planted Aquilaria plantations, or will they undermine investment in the plantation approach?

Cultural and Biodiversity Considerations

Agarwood has been used for millennia in Buddhist, Hindu and Islamic ceremonies, and also in Chinese, Tibetan and Ayurvedic traditional medicine. Throughout Malaysia the Orang Asli (the area's First or indigenous peoples) are reportedly the most important collectors and primary traders of agarwood.[15] As global demand grows for high-quality agarwood some species are now nearing extinction in the wild.[16] Because of its threatened status, since 2004 trade in all wild *Aquilaria* species is controlled under Appendix II of the Convention on International Trade in Endangered Species (CITES) of Fauna and Flora.[17]

Not all *Aquilaria* trees contain the valuable resinous deposits, and most people can't tell if a tree contains the resin without felling the tree and cutting it open – actions that further endanger the wild *Aquilaria* trees.

In response, the Malaysian Forest Research Institute Malaysia (FRIM)[18] and private sector investors have established *Aquilaria* plantations;[19] but techniques for inducing resin formation in plantation-grown trees reportedly yield lower-quality agarwood than wild-harvested trees.[20] This could change with research. Beginning in the late 1990s, FRIM collaborated with a New Zealand research company, Industrial Research Limited, to establish trial plantations. In 2015, Singapore-based Asia Plantation Capital (APC) acquired 260 acres of land in Malaysia for the planting of two agarwood plantations, and also opened a new agarwood processing factory and research centre, in Johor, Malaysia.[21] In addition, APC operates existing agarwood plantations in China, India, Sri Lanka, Myanmar and Thailand. The company aims to be the industry leader in the agarwood market. Those managing large-scale plantations argue that agarwood plantations are more sustainable than cutting wild *Aquilaria* trees.

Synthetic Biology Production

In June 2014, a Swiss synthetic biology company, Evolva, announced that it is collaborating with the Malaysian Biotechnology Corporation and Universiti Malaysia Pahang to develop engineered yeast that can produce some of the aromatic compounds found in Agarwood. According to Evolva: "The goal is to create a new paradigm in the sustainable production of Malaysia's high value indigenous natural products, starting with agarwood fragrances."[22]

There is no timetable for commercialization. Evolva's 2014 annual report says the status of agarwood-related research is at the "pathway construction" stage.[23]

Efflorus is a Canadian synthetic biology start-up also working on producing oud oil. Efflorus believes their "bio-oud" will be on the market by 2017. They are also working towards other rare fragrances like Musk (source – Musk Deer) and Ambergris (source – sperm whales/clary sage).[24]

Implications and the Future

Evolva makes a compelling case that biosynthesis of agarwood's aromatic compounds offers a more sustainable approach than illegal cutting of endangered trees. Given that wild *Aquilaria* trees are increasingly rare, will synthetic biology enable Malaysia to create a sustainable market and save the forest?

Will the aroma compounds produced by engineered microbes in fermentation tanks be able to compete with newly planted *Aquilaria* plantations, or will they undermine investment in the plantation approach? Evolva's website states that the company's syn bio platform will allow Malaysia to "widen the use of agarwood worldwide" and "complement the existing traditional production approaches."[25] It remains to be seen if Efflorus or Evolva and its partners can produce a commercially viable product via biosynthesis, and how that might affect the global market.

There is not yet a meaningful discussion about the impact that the transition from wild harvesting and plantation production to synthetic production may have on traditional collectors or plantation workers. Similarly, there is cause for concern that a shift from plantation production to synthetic production could negatively affect plantation workers.

Endnotes

1 www.asiaplantationcapital.com/products/agarwood

2 Nineteen agarwood-producing species have been reported. Source: R. Naef, "The volatile and semi-volatileconstituents of agarwood, the infected heartwood of *Aquilaria* species: A review," *Flavour and Fragrance Journal,* 26, 73–89 (2011). regula-naef@bluewin.ch Natural forests in all three regions of Malaysia (Peninsular Malaysia, Sabah and Sarawak) remain important sources of agarwood in international trade.

3 The aromatic resin is produced naturally by Agarwood trees as a defense/healing mechanism when they are attacked by infection or pests.

4 Michael Zviely, and Ming Li, "Sesquiterpenoids: The Holy Fragrance Ingredients," *Perfumer & Flavorist,* Vol. 38, June 2013.

5 Including India, Myanmar , Laos, Vietnam and Cambodia to Malaysia, Sumatra, Borneo, the Philippines and Papua-New Guinea.

6 Malaysia made up about 50% of the total reported volume of agarwood declared in CITES trade internationally in 2005.

7 Studies have shown that even though many Orang Asli communities no longer collect as much gaharu (or agarwood oil) as they did 10 years ago (C. Nicholas, pers. comm. September 2005), prohibition on unlicensed collection and enforcement of the required licensing would have a significant effect on the income of certain groups, possibly exacerbating poverty.

8 Dr. Pakamas Chetpattananondh, "Overview Of The Agarwood Oil Industry, International Federation of Essential Oils and Aroma Trades (IFEAT)," *Proceedings of the IFEAT International Conference 2012.* www.ifeat.org/wp-content/uploads/2013/02/Singapore_Proceedings_lowres.pdf

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12 According to Asia Plantation Capital, the trade figures are from TradeMap.org www.asiaplantationcapital.com/products/agarwood

13 Md. Joynal Abdin, "The Bangladeshi Agarwood Industry: Development Barriers and a Potential Way Forward," Bangladesh Development Research Working Paper Series (BDRWPS 22) June 2014. www.researchgate.net/profile/Md_Joynal_Abdin/publication/263468435_The_Bangladeshi_Agarwood_Industry_Development_Barriers_and_a_Potential_Way_Forward/links/0c96053afdbccc8ea0000000.pdf

14 According to Asia Plantation Capital, the trade figures are from TradeMap.org www.asiaplantationcapital.com/products/agarwood

15 Lim Teck Wyn and Noorainie Awang Anak (2010). “Wood for trees: A review of the agarwood (gaharu) trade in Malaysia.” TRAFFIC Southeast Asia.

16 *Ibid*.

17 Under Appendix II of CITES, agarwood trade is regulated under a system of permits based on conditions of legality and sustainability – but regulations are not implemented or enforced in all areas.

18 The Forest Research Institute Malaysia (FRIM) has long recommended the establishment of commercial *Aquilaria* plantations as a more sustainable solution for agarwood production.

19 Beginning in the late 1990s, for example, FRIM collaborated with a New Zealand research company, Industrial Research Limited.

20 In 2005 Malaysia planted agarwood trees on 40 ha of land in Mercang. Rosli Zakaria, “Agarwood’s value is also its curse,” *New Strait Times Online,* 4 November 2014. www.nst.com.my/node/49379

21 www.asiaplantationcapital.com/plantations/malaysia

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25 Evolva News Release. “Malaysian Biotechnology Corporation, Universiti Malaysia Pahang and Evolva collaborate to establish centre of excellence for Malaysian Natural Products,” June 4, 2014. www.evolva.com/media/press-releases/2014/6/4/malaysian-biotechnology-corporation-universitimalaysia-pahang-and

Ambergris & Clary Sage Oil

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: 120 Family farms in NC, USA. More in China, Ukraine and France.

Market Value: $13,6 -18,2 Million US[1]

Uses: Fixative & fragrance in perfumes and household products (laundry detergent, fabric softener, dish soaps)

Syn bio Companies: Efflorus, Firmenich, Evolva, Amyris

Hotspots: North Carolina (USA), China, France, Hungary, India

Also Grown In: Crimea, Ukraine and Caucasus regions bordering the Black Sea, Bulgaria, Italy, Morocco, Romania and England.

Cultural Importance: Descriptions of medicinal use of clary sage goes back to the writings of Pliny the Elder (1st century CE). Used widely in perfumes and as a muscatel flavoring for vermouths, wines, and liqueurs. Ambergris is historically one of the most prized scents in perfumery, eg. Chanel Nº 5.

Biodiversity Considerations: The flowering plants have benefits for pollinators, and sage is eaten by many species.

Quality Concerns: Natural ambergris and sage oils have many chemical constituents - syn bio companies usually manufacture only one component of the natural product, not all the molecules present in the natural product.

Patents: Method for producing Sclareol Patent #9267155, # 8617860, #8586328 (Firmenich - Michel Schalk Inventor) US20100311134, EP2569427A1, US8927238, US20150099283, WO2011141855A1

Products: Sclareol, Ambroxide

Brands, Identifiers: Ambrox®, "Sclareol Bio"

Method: Synthetically engineered yeast and *E. coli* bacteria

Commercialization: Should be on the market in 2016, already produced

Feedstock, Biomass: Sugarcane

Overview

While high-end perfumers may still use the expensive and hard-to-find substance ambergris, which is produced in the intestines of sperm whales, most of the industry now uses a substance known as "ambroxide," synthesized from the compound "sclareol" found in clary sage oil. Ambroxide is used both as a fragrance and as a "fixative" for making scents linger longer in products.

Status: Syn bio ambergris may be available in 2016

R&D — Scale Up — Commercialization

Clary sage, a flowering herb with biodiversity benefits, is commercially grown in North Carolina US, as well as in France, China, Crimea and Ukraine. As at least 3 synthetic biology companies are working towards commercializing a syn bio-derived version of ambergris and/or clary sage oil. Ahead of the pack is flavours and fragrance giant Firmenich, partnered with syn bio company Amyris. Firmenich has announced that their syn bio ambroxide will be commercially available during 2016. Amyris appears to have already shipped 100 tons of syn bio clary sage oil from their Braziliian production facility.

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

What is Ambergris / Clary Sage Oil (*Sclareol*)?

Ambergris is a grey waxy substance, a bile secretion found in the digestive tract of some sperm whales. It has been prized in the fragrance and perfume industry for its delicate odor and fixative properties. Combined with perfume, soaps and detergents, it can intensify and extend scents on such products. Its key chemical constituent is ambroxide. Since natural ambergris is hard to find and hugely expensive, the industry today uses a synthetic version of ambroxide (brand name Ambrox) derived from sclareol - the key compound extracted from clary sage plants *(Salvia sclarea)*. Clary sage is a flowering herb originally native to Europe. Small amounts of ambroxide can also be used as a food flavouring ingredient.

Ambergris / Clary Sage as a Natural Product

Natural ambergris is a bile duct secretion from a small percentage of sperm whales and is generally discovered by chance on beaches or floating in the sea - it is a rare and highly valuable find. In 1986 the International Whaling Commission instituted a moratorium on commercial whaling. Although ambergris is not currently harvested directly from whales, many countries also ban its trade as part of the more general ban on the hunting and exploitation of whales.[2] This has led to supply shortage and price inflation, so perfume makers have turned to substitutes. Clary sage has been commercially cultivated in China, France, Hungary, India, Bulgaria, Italy, Morocco, Romania, England and Ukraine, the Crimean and Caucasus regions bordering the Black Sea. Today however, North Carolina in the USA is the world's largest producer of clary sage oil and sclareol. One North Carolina company, Avoca Inc. - spun out of tobacco giant RJ Reynolds - claims to be the world's primary manufacturer and supplier of sclareol to the fragrance industry, supplying 90% of global clary sage oil. The company has contracted 120 local farmers in 11 counties of North Carolina to grow 25,000 acres of clary sage.[3]

Farmers get paid according to the pounds of scareol per load.[4] Avoca sells about 10% of sclareol for use in fine fragrances, and about 90% enters household products.[5]

Parrish Farms, a family-owned farm corporation in Chowan County, was among the first sage growers in North Carolina. Today, the fourth-generation farm family grows 400 acres of sage, a sizable percentage of their 2,200 acres. They also grow peanuts, cotton, soybeans and wheat, which experience wild price swings. Their sage rotation, however, brings stability, since the price has stayed steady for 15 years.

"It's probably one of the most stable crops that we grow. Clary sage is the backbone of our farming operation and has been for years. It's something we can count on."
Parrish Farms, North Carolina

Parrish says: " It's probably one of the most stable crops that we grow. Clary sage is the backbone of our farming operation and has been for years. It's something we can count on."[6]

The Ukraine and Crimea were previously significant producers of clary sage essential oil. These countries supplied 80% of Russian essential oil production (coriander, clary sage, fennel seeds and others) from 4,000 hectares in two small regions.[7] Since 2014 however, political instability, turmoil and fighting have disturbed essential oil production in this region, including clary sage.

Biodiversity and Cultural Considerations

Clary sage has long been used medicinally, particularly for improving vision and eye health, and is related to common garden sage. Clary sage oil is sometimes called "Muscatel Oil" because of its use flavouring muscatel wine. As a flowering herb, its production has important biodiversity benefits, supporting pollinators and contributing to natural pest control management.

Promoting bee population and pollinator habitat increases the availability of pollen and nectar resources, and provides secondary benefits to the farms and surrounding landscapes. Contribution to a pollinator habitat enhances overall biodiversity and the ecosystem services it provides, as well as contributing to rural aesthetic.[8]

Synthetic Biology Production

Since natural yields for clary sage may be variable, and manual collection of ambergris is highly unpredictable and expensive, the fragrance industry has been looking for a cheaper and more reliable alternative means for producing ambroxide and sclareol.

Two Swiss firms, Firmenich and Evolva, have separately developed new, synthetic biology organisms that produce sclareol. Scientists working for fragrance giant Firmenich have engineered E. coli bacteria to produce sclareol, which can then be turned into ambroxide.[9] They have also collaborated with syn bio company Amyris, which uses engineered yeast for production. This new version of Ambrox, obtained through synthetic biology, has been scheduled to hit the market in 2016, as announced by Firmenich in a press release dated February 2016.[10] Customs records show that in the first 2 months of 2016 Amyris shipped around 100 tonnes of "Sclareol Bio" from its syn bio biorefinery in Brazil - presumably for sale by Firmenich. In past years, 100 tons was equal to entire global production.

Evolva, which uses yeast as the basis of their synthetic biology process, are also developing a syn bio-derived ambroxide, but no timeline for commercialization has been provided. This work may be part of their partnership with the Japanese fragrance corporation Takasago International.

Additionally, Efflorus, a Canadian start-up mentored and funded by the US-Irish IndieBio Accelerator, is also working on ambergris, musk deer and oud oil. Commercialization dates are unknown.[11]

Implications and the Future

It is not yet clear how Firmenich's imminent commercialization of syn bio-derived ambroxide could impact clary sage growers. Firmenich appears to be putting considerable marketing behind the new version of Ambrox, describing it as the result of "green chemistry"; and the recent shipment of 100 tons of sclareol from Amyris makes it clear that significant amounts of bioengineered oil is coming to market to compete with natural sage oil.

Endnotes

1 Based on 100 tons x 150-200 US$/kg

2 https://en.wikipedia.org/wiki/Ambergris

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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.

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

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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

Ginseng

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: Exact numbers are difficult to obtain; many thousands

Market value: $2.1 billion US including processed goods (2009)[1]

Volume: Approx. 72,600 tonnes/year[2]

Uses: Traditional medicine, food

Syn Bio Companies: Evolva, Amyris

Hotspots: China, South Korea, Canada, USA

Also Grown In: Bhutan, some European countries, Oceania

Cultural importance: Used for over 4,500 years in Eastern medicine to counter stress, disease and exhaustion

Biodiversity Considerations: Ginseng is grown under shade in natural or artificial forests which supports agroforestry. Crops with high value per acre tend to decrease pressure to exploit local biodiversity.

Quality Concerns: Botanical ginseng has at least 40 chemical constituents. Syn Bio Companies target a narrow range of ginsenosides and therefore benefits of natural ginseng may not apply.

Patents: CN 102925376 B, KR100931845 (B1), WO 2012070724 A1

Method: Synthetically engineered yeast

Commercialization: Still at proof of concept stage. Currently no announced commercialization, but there may be a Chinese product already available.

Feedstock: Biomass

Brands, Identifiers: Xinseng

Overview

The hairy root of the ginseng plant (*Panax ginseng*) has been used for over 4,500 years in eastern medicine to counter stress, disease and exhaustion. It is especially highly prized in South Korea. Since the 19th century, a North American variety, (*Panax quinquefolius*), with similar effects, is also widely grown and used. It is also eaten as a food. Ginsenosides are active compounds only found in ginseng that have a number of health-related effects. Approximately 40 ginsenoside compounds have been identified.[3]

Status: Syn bio ginseng is still under development

R&D — Scale Up — Commercialization

There are active research projects in Belgium and China successfully using synthetic biology to produce some of these 40 ginsenosides in engineered yeast and in other plants. Additionally, Swiss synthetic biology company Evolva Inc. has confirmed that it is targeting ginseng as a commercial product.

What is Ginseng?

Panax Ginseng is an Asian root crop widely used in health foods for its wide range of claimed medicinal properties. The key compounds in ginseng are known as ginsenosides. Approximately 40 ginsenoside compounds have been identified.[4] Ginseng is a slow-growing herbaceous forest plant whose roots are said to resemble the shape of a person (hence “ginseng” means “person root”).

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

Together, South Korea, China, Canada and the US account for over 99% of the global ginseng harvest. Culturally, ginseng is most significant for South Korea, the world's largest consumer as well as its second largest producer. The North American variety, *Papanax quinquefolius* is grown in Canada and the US mostly for the oriental market, although it does not command as high a price.

Ginseng as a Natural Product

Approximately 72,600 tonnes[5] of botanical ginseng are produced annually worldwide with production almost entirely in four countries (China, South Korea, Canada and USA). China is the world's largest producer with annual production of 40,596 tonnes. It is followed by South Korea (24,929 tonnes), Canada (5,884 tonnes) and the US (956 tonnes).. The world ginseng market –including ginseng root and processed products–is estimated to be worth $2.1 billion US; the size of the Korean market alone is $1.1 billion US, of which $38 million US are exported.[6] Growing a ginseng root for harvest takes 4-6 years and requires that a new root is planted on naturally or artificially-shaded soils that did not have ginseng the previous year. Successful ginseng farming is difficult and requires skill. In an effort to circumvent growing challenges and assure availability of ginsenosides for foods and medicines, there has already been considerable research and development of laboratory cell cultures for ginseng. A few tonnes of tissue-cultured ginseng are currently being sold in the Korean market, but the technique is low-yielding and the bulk of production remains overwhelmingly botanically-derived.[7] The arrival of synthetic biology techniques may mark a new techno-rival for ginseng farmers.

Biodiversity and Cultural Considerations

Ginseng originally was wild-harvested and is a shade-grown crop and therefore fits very well into agroforestry systems that preserve natural forested landscapes. It is also a crop that encourages hand labor, as opposed to the frequent use of machinery and chemical inputs. The long-term, labor-intensive farming used to grow ginseng, especially the "wild-simulated" method, does not have the adverse effects of industrialized farming. It can be considered less disruptive of the environment and surrounding biodiversity. Moreover, crops with high value per acre tend to increase local wealth and to decrease pressure to exploit local biodiversity. For Chinese and Korean society in particular the cultural value of ginseng cannot be overstated; the gnarly root is one of the iconic images of South Korean culture. With a long history of medicinal use and claimed medical benefits,[8] particularly for boosting memory and energy levels, wild ginseng was keenly hunted for and there are many folk tales of this "person-root" coming alive.[9]

Synthetic Biology Production

Ginseng is now receiving attention from synthetic biologists interested in engineering microbes and crops to replace the *Panax Ginseng* plant grown in the Orient. The focus of interest are various ginsenosides that accumulate in the ginseng root. The compounds of most interest are known as Rb1, Rb2, Rc, Rd, Re, Rf, Rg1 and Ro; they are from a class called Triterpenoid saponins, which are known as "isoprenoid compounds." A number of research groups and private companies (Amyris, Evolva, Isobionics) have already built and commercialized synthetic organisms able to produce other isoprenoids in vats. As another commercially valuable isoprenoid, ginsenosides, are now becoming an attractive industrial target. At least three research teams and one commercial company have set their sights on producing synthetically-derived ginsenosides by using synthetic microbes created for this purpose. In 2012 a team of bioengineers from Jilin University in China engineered bakers' yeast to produce the compound dammarenediol, which is the key precursor for ginsenosides.[10] The researchers report that "engineered microbial systems producing ginsenosides or a ginsenoside precursor... should facilitate practical production of ginsenosides by providing an inexpensive and environmentally benign alternative to extraction from ginseng roots." In an online marketing presentation, the research team boasted that unlike the 6 years required to grow natural ginseng, their product "Xinseng" will take only a few days to produce through their patented synthetic biology processes.[11]

They claim Xinseng will be available as a powder, in capsules or liquid form, as "a substitute for cultivated ginseng." It is not clear if "Xinseng" is already commercialized.

Another Chinese team published a paper in *Nature* in January 2014 showing that they had also engineered yeast to produce three key ginseng precursor compounds (Protopanaxadiol, protopanaxatriol and oleanolic acid). They boasted that "The yeast strains engineered in this work can serve as the basis for creating an alternative way for producing ginsenosides in place of extractions from plant sources."[12]

A Belgian team at the University of Ghent is developing a combinatorial synthetic biology platform to engineer yeast as well as clover plants to produce a variety of key compounds, including ginsenosides.[13] According to the group's home page, they hope to serve the needs and demands of the pharmaceutical, agrochemical and nutraceutical industries. At the same time, leading synthetic biology company Evolva of Switzerland has an active interest in engineering yeast to produce ginseng compounds.

In its presentations to investors, Evolva lays out a full list of natural products that it aspires to replace, including ginseng,[14] and has confirmed to ETC Group that it is actively working on ginsenosides. Much of Evolva's partnership with food, cosmetic and ingredients companies is to develop undisclosed compounds for their private clients, so it is not known if Evolva's work on ginsenosides is part of an agreement with other companies.

Another synthetic biology company that currently produces isoprenoids and may be well placed to develop syn bio-derived ginsenosides is Amyris Inc of California. Amyris already commercially sells a syn bio-derived squalane - a substance that can be converted biochemically into ginsenosides. Like Evolva, Amyris is also developing undisclosed compounds for private companies to commercialize.

Implications and the Future

Currently, there is no concrete evidence that a syn bio version of ginseng is poised to enter the market. However, with several teams working to create such a product all the elements show that a syn bio ginseng could soon emerge that might impact the market for this iconic crop and the farmers that grow it.

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Patchouli Oil

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: Around 12,000 farm families involved in cultivation; a further 2,000 employed in distillation; 300 in the collection trade[1]

Market Value: $100 million US[2]

Uses: Perfumes, soaps, cosmetics, incense, scented products

Syn Bio Companies: Amyris in partnership with Firmenich, Isobionics

Hotspots: Indonesia

Also Grown In: China, India, Malaysia, Singapore, Philippines

Cultural Importance: Used for centuries in traditional medicine in Malaysia, China and Japan, also as a fumigant, insect repellent and to sooth snake / insect bites

Biodiversity Considerations: Wild-grown, native perennial crop; good for intercropping

Quality Concerns: Natural patchouli oil has many constituents. Syn bio companies manufacture only a single molecule.

Patents: METHOD FOR PRODUCING PATCHOULOL AND 7-EPI-ALPHA-SELINENE

Patent number: EP2569427A1, US8927238, US20150099283, WO2011141855A1 (Firmenich)[3]

Products: Patchouli oil

Method: Synthetically engineered yeast

Commercialization: Firmenich's Clearwood™ is on the market. Isobionics' patchouli oil is still under development.[4]

Feedstock: Sugar cane

Brands, Identifiers: Clearwood™

Overview

Popularly associated with the hippie counterculture of the 1960s and as an iconic "Asian" scent, natural patchouli oil is extracted from a species of the mint family called *Pogostemon cablin*. It thrives in Indonesia, Malaysia, Philippines and South Asia and supports around 12,000 farm familes. Besides perfumes, patchouli is commonly added to detergents, soaps, candles and other common household products.

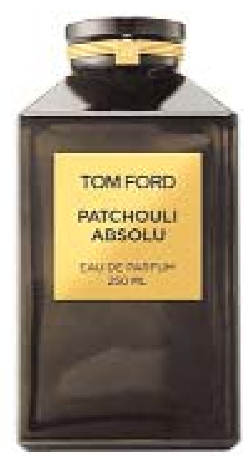
Status: Syn bio patchouli is already on the market

R&D — Scale Up — Commercialization

The key constituent of the oil is patchoulol, which has now been produced using synthetically engineered yeast by California-based biotech company Amyris, in partnership with Firmenich, a Swiss purveyor of perfumes and flavours. Their patchouli ingredient is tradmarked Clearwood™ and is already incorporated into leading fragrances. A Dutch synthetic biology ("syn bio") company, Isobionics, is also threatening to soon commercialize a syn bio form of patchouli oil.

What is Patchouli Oil?

Patchouli (meaning "green leaf" in old Tamil) or *Pogostemon cablin* is a perennial species of the mint family that thrives in the wild in warm tropical climates, especially in Indonesia.



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

Originally used as in eastern medicine and to protect cloth from insect damage, its distinct odour became closely associated with the "hippie" counterculture of the 1960s. Its fragrance was widely used by young people in perfumes and incense to invoke the mysterious East. Patchouli oil is key to a class of perfumes (the chypre fragrances) and is today widely used in laundry detergents, air fresheners, candles, soaps, baby wipes and other household scented products. It is also commonly used in pharmacy and cosmetics as a very efficient antimicrobial ingredient. Its principal component is called patchoulol.

Patchouli as a Natural Product

Although patchouli originates in the Philippines and India (Tamil Nadu), Indonesia is the world's largest producer of patchouli, accounting for over 80% of the global market. Historically, Java and Sumatra were key growing regions for the oil, but these areas now account for only 20%, with almost no raw material coming from Java. Today Sulawesi (Indonesia) is the primary growing region. Patchouli crops cannot be grown on the same patch of land for long periods, so plantations need to be moved to different areas every 5 years.[5]

Current annual production of patchouli oil is volumes are around 1,000-1,200 metric tonnes, with market demand calculated to be around the same. Secondary suppliers are China, India and Malaysia. Patchouli oil can fetch $40-70 US per kilogram. According to IFEAT (International Federation of Essential Oils and Aroma Trade), Indonesia produces around 1,200 tonnes per year, with a value of around $70 to $100 million US. According to IFEAT, a typical patchouli farm family in Indonesia owns in the range 0.25 to 1 ha of land and produces 25 to 100 kg of patchouli oil per year. Around 12,000 farming families are involved in cultivation (amounting to around 50,000 supported individuals). A further 2,000 people are employed in distillation and 300 in the collection trade.[6]

Cultural and Biodiversity Considerations

As mentioned, patchouli was used for centuries in traditional medicine in Malaysia, China and Japan, as well as a fumigant, insect repellent and remedy for snake and insect bites. It was added to cloth and textiles exported along the silk route to protect them against insect damage, and thereby gave these imports a distinctive "oriental" scent. This connection added to its popularity in the 1960s and 1970s with the hippie counterculture.

As a wild-grown crop as well as a perennial, patchouli is closely linked to biodiversity considerations. Long-term perennial crops provide the advantages of a stable environment partly because the cultivation of such crops is based on long-established traditional varieties, held in balance with the surrounding flora. Wildcrafted crops thus help support the maintenance of natural ecosystems and their complex flora and faunana.[7] According to the United Nations Environment Programme (UNEP), patchouli is suitable for intercropping and diversification of crops. It is also important as alternative crops in areas taken over by monoculture production, as has been seen most recently with palm oil plantations and rubber production in Sumatra.[8]

Synthetic Biology Production

Following weather-related supply chain problems with sourcing patchouli, the fragrance industry took a strong interest in finding a synthetic version of this oil. Patchoulol, the key component of patchouli oil, has now been produced commercially through synthetically altered yeast developed by the California-based biotech company Amyris, in partnership with Firmenich, a Swiss purveyor of perfumes and flavours. The companies have already produced large volumes of patchouli oil fermented on sugarcane in Amyris's facility in Brotas, Brazil. Firmenich sells this oil to perfumers and product manufacturers as the scent Clearwood™, which is described as a "woody ingredient with clean patchouli scents."

The product is already in use in consumer goods and leading perfumes such as Tom Ford's "Patchouli Absolu." When the fragrance won a recent award, Firmenichs master perfumer Harry Fremont claimed, "This breakthrough ingredient is revolutionizing how perfumers play with the patchouli character, to create totally modern fragrance creations for men and women."[9]

A second synthetic biology company, Isobionics in the Netherlands, has also developed its own version of patchouli oil and claims it is scaling up production to bring it to market soon.[10]

Implications and the Future

While global agriculture is increasingly dominated by large-scale industrial production, the production of most essential oils is still dominated by small farmer production, and as such makes an important contribution to the incomes and livelihoods of relatively poor rural populations in developing countries.[11] The smallholders and small farmers of Indonesia, Malaysia, China, and Singapore will inevitably be affected by the introduction of Clearwood™ and forthcoming products from isobionics. With Clearwood™, Amyris is able to replace the lengthy cultivation and extraction process with a single manufacturing process that produces patchouli oil in about two weeks. Even if the resulting product is synthetically obtained and may not possess exactly the same qualities as the natural oil, the ease of production undercuts the farmer's efforts tremendously and will also impact the consumer's future ability to get true patchouli.

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Rose Oil

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: 75,000 in Turkey and Bulgaria

Volume: 3,000 to 4,500kg/year[1]

Market Value: Exports are valued at 15 million euros[2]

Uses: Perfumes and Cosmetics

Syn Bio Companies: Ginkgo BioWorks in partnership with Robertet, Celbius

Hotspots: Bulgaria (Kazanlak, Karlovo, Streltcha, Zelinkovo and Chirpan regions) and Turkey (southwest province)

Also Grown In: Morocco, Iran, Mexico, France, Italy, Lebanon, India, Russia, China, Ukraine and Crimea. New producers emerging in Afghanistan, Saudi Arabia and Egypt

Cultural Importance: Oil-producing roses of Bulgaria are national symbol linked to tourism, festivals and traditional events.

Biodiversity Considerations: Bred in regions which can not be effectively used for other agriculture. Flowering plants aid natural pest control management. Promotes bee population and pollinator habitat.

Quality Concerns: Because of its complexity, no one has been able to synthesize the true scent of damask roses. It is unlikely that a syn bio product, which is always hampered by molecules of only a few components, will be able to duplicate it.

Commercialization: May already be on the market

Overview

Rose oil[3] – a classic ingredient in perfumes and cosmetics – is the essential oil distilled from freshly harvested rose petals (*Rosa damascena*).[4] Although many molecular components of rose oil have been chemically synthesized, scientists have been unable to match the complex scent of the essential oil derived from Damask roses.[5]

Status: Syn bio rose oil may already be on the market

R&D — Scale Up — Commercialization

Now, several syn bio companies, in Boston, the UK and China, are researching and developing syn bio engineered yeast microbes to produce rose scents. Leading the pack is Boston-based Ginkgo Bioworks whose syn bio-derived version of "rose oil" will be commercialized by leading essentials oil producer Robertet.

What Is Rose Oil?

Rose Oil is a perfume and cosmetic essential oil made from rose petals. The most valued variety is *Rosa damascena*, the Damask rose, a very old type. The oil is distilled from the flowers, requiring many workers to care for and pick the plant, and is an important commodity, especially in Bulgaria and Turkey, but also in China, France, Lebanon and Afghanistan. Although many parts of the rose scent have been synthesized for years, industry has not been able to duplicate the true rose fragrance, which is very complex and is worth thousands of dollars per kilo. This is why it's a tempting new product for synthetic biology engineers, who are working on creating novel forms of yeast that will produce rose-like odors.

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

Rose Oil as a Natural Product

Rose oil is one of the world's most expensive essential oils,[6] used and appreciated for thousands of years. Today it is produced mostly in Bulgaria and Turkey, but many other countries, including China, France, Lebanon and Afghanistan are also producers. High-quality Bulgarian rose oil was priced at $5,750 US per kg in 2014.[7] The harvest is labor-intensive: it takes 1.25 million hand-picked flowers[8] and about 800 worker hours to produce 1 kg of rose oil. The fragrance/flavor industry, cosmetic and perfume companies are the largest buyers of rose oil. Worldwide production of rose oil ranges from 3,000 to 5,000 kg per annum.[9]

Bulgaria and Turkey, where rose cultivation is centuries old, account for about 80%-90% of rose oil production worldwide.[10] The rose oil industry employs over 75,000 farmers and seasonal harvest workers in these two countries alone. Other rose oil and rose water[11] producing countries include Morocco[12], Iran, India, China, France and Russia. New producers are emerging on the market in Afghanistan, Saudi Arabia and Egypt.[13]

In southwest Turkey, about 12,000 small farmers produce oil-bearing roses on approximately 2,300 ha.[14] Turkey's rose oil exports were valued at $12.6 million in 2012 (940 kg of rose oil; 6900 kg of rose concrete and 1,020 kg of rose absolute).[15]

Bulgaria exports an estimated 1,500 to 1,800 kg of rose oil annually[16] from damascena roses grown on approximately 3,500 ha in the Rose valley regions of Kazanlak and Karlovo.[17] The Bulgarian rose oil industry employs an estimated 65,000 workers – 50,000 of them seasonally.[18] Production is divided almost evenly between plantations (owned by distillers) and small farmers.[19] Bulgarian rose oil exports are valued at approximately $9-$11 million per annum.[20] Bulgaria's exports of all essential oils were valued at $35.2 million in 2012.[21]

Cultural and Biodiversity Considerations

Sustainable tourism driven by the rose sector is of economic importance for Bulgaria. Bulgarian roses and rose oil are an important symbol of national identity and pride. This is not only due to their unique geographical origin traced to the Rose Valley, but also due to the distinctive social and cultural capital of the people involved in the process and development of skills, techniques, traditions, rituals, and diligence in growing roses and producing various rose-derived products.[22] Festivals and traditional events drive national and international tourism during May and June.

Currently industrial production uses agrochemicals . However, there is increasing acreage of organic production of rose petals. As a flowering plant such crops can be beneficial for pollinators. Like any labour-intensive, high-value product, the crop tends to favour biodiversity and long-term soil management.

Synthetic Biology Production

Ginkgo BioWorks, a USA-based synthetic biology company, is partnering with fragrance/flavor company Robertet (France) to engineer yeast microbes that biosynthesize the production of rose oil compounds. Robertet is one of the world's largest buyers and processors of rose oil.

According to an article published in Fortune magazine of July 2015, Robertet's and Ginkgo BioWorks' rose oil is already on the market, sold as a perfume.[23] Although Ginkgo BioWorks holds a number of patents and patent applications related to microbial biosynthesis, published patents do not specifically refer to rose oil biosynthesis.[24]

Robertet (France) is the 10th largest flavour and fragrance company (2013 sales: $536.6 million). The company describes itself as a "global leader in natural ingredients." Robertet operates rose oil processing facilities in Bulgaria and Turkey – the world's two largest producers of roses used for extraction of rose oil (or its by-products). Robertet's self-professed motto is: "Natural, always natural." However, although a Fortune article mentioned above says the syn bio rose oil is for sale, nowhere on the Robertet or Ginkgo BioWorks websites is that verifiable.[25]

Gingko BioWorks, which describes itself as "an organism engineering company," reportedly has 20 contracts with companies to develop syn bio flavors, fragrances, cosmetics, sweeteners and natural pesticides.[26] The company's partnership with the all-natural Robertet to produce rose oil compounds in engineered yeast is one of the few targets announced publicly. CEO Jason Kelly told the Boston Globe that he expects the first products made by Ginkgo-crafted organisms "to be sold by our partners by the end of the year, or first quarter of 2016."[27]

The new rose oil may not even come from roses. In 2015, Patrick Boyle of Gingko BioWorks told New Scientist:

"Our goal is to recreate the rose biosynthetic pathways, even if we don't use rose genes to do it...We often find that a different but highly related gene from a different species works better in yeast than the rose gene that has the function we want."[28]

In his remarks before the 2014 annual meeting of the International Federation of Essential Oils and Aroma Trades, Jason Kelly of Ginkgo BioWorks stated that his company's goal is not to replace existing ingredients but to provide "creative opportunities" such as a rose oil that is chemically distinct from its botanically-derived counterpart.[29] Ginkgo claims on its website that "instead of just limiting ourselves to what naturally-occurring roses provide," the company's custom-made microbes will "expand the variety of rose oil and rose scents even further."[30]

Besides this effort, scientists at the Jiao Tong University in Shanghai, China are also conducting research on the biosynthesis of rose essential oil.[31] Celbius, an industrial biotechnology based in the UK, has developed the production of 2-phenylethanol (2PE) using synthetic biology. 2PE is an aromatic alcohol with rose-like odour and is used in the food, drink and cosmetic industry, particularly when the smell of rose is desired. 2PE occurs widely in nature, being found in a variety of essential oils, including rose. Its floral odour means it is used in flavour and perfumery, also as a preservative in soaps due to its antimicrobial properties.[32]

Implications and the Future

Rose oil extracted from harvested petals of *Rosa damascena* contains at least 8 major chemical compounds[33] and more than 275 minor constituents.[34] It is unlikely that synthetic biology companies will be able to replicate the complexity of rose oil molecules extracted from damask flowers. However, it won't be necessary to fully duplicate the molecular composition in order to disrupt the global market for botanically-derived rose oil – especially if much lower-priced rose-scented oil and by-products are offered. It is too soon to predict if Ginkgo BioWorks or some other company will be able to engineer microbes to biosynthesize aroma molecules that are comparable to rose oil.

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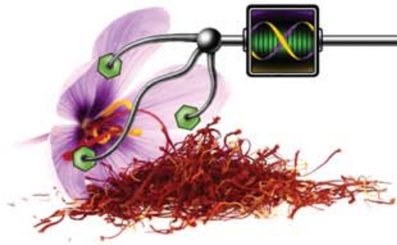

Saffron

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: 150,000 farmers in Iran[1], 16,000 farmer families in Kashmir[2], 5,000 in Greece, 6,000 in Afghanistan, 1,200 in Morocco

Market Value: $660 million US annual sales - Based on current average market prices of $2,000 US/kg[3], 270 tonnes worldwide

Uses: Food, flavour, colour, medicine, perfumery

Syn bio Companies: Evolva

Hotspots: Iran (240 Tons/year)

Also Grown In: Greece (7.5 tons/year), India (Cachemire) (2.3 tons/year), Morocco (2.3 tons/year), Spain (1 ton/year), China (1 ton/year), Turkey, Kashmir and Afghanistan, Azerbaijan, Italy

Cultural Importance: Important religious, spiritual, medicinal, dietary and royal meanings. Drives tourism and represents local cultural identity and skills.

Biodiversity Considerations: Low water requirement, promotes pollinator population and habitats (natural pest control management and increased overall ecosystem services)

Quality Concerns: Natural saffron has at least 7 chemical constituents, and there are clear differences between the components of saffron grown in Iran and saffron grown elsewhere. Evolva are only synthetically producing a few constituents of saffron.

Patents: WO2015002528 A1, US20140248668 A1, US 7691406 B2, WO 2013021261 A2, WO/2015/162283, 20150093776

Products: None as yet

Method: Synthetically engineered yeast organisms

Commercialization: To be partnered, will delay launch to 2017 or later

Feedstock: Biomass

Brands, Identifiers: Unknown

Overview

Known for its rich scent and brilliant red and orange hues, saffron is the world's most expensive spice by weight. Saffron itself is the stamen, that is, the part where grains of pollen germinate, of the flower *Crocus sativus.* It is used in a variety of dishes, baked goods and liquors. Due to its high labor requirement, saffron is known to employ on average 200 person/days per hectare, employing a large percentage of women (80%). Its production affects more than 150,000 farmers in Iran, 16,000 in Kashmir, 6,000 in Afghanistan.[5]

Status: Syn bio saffron may be on the market in 2017

R&D — Scale Up — Commercialization

Evolva, a Swiss synthetic biology company, has successfully completed an R&D process to create bioengineered yeast that produce the key chemical compounds in saffron related to colour and flavour. Evolva is now able to make these compounds through fermentation of engineered yeast, bypassing the need for growing crocus flowers.

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

What is Saffron?

Saffron is the tiny harvested stamens of Crocus sativus, a widely grown variety of wildflower. Saffron is prizedd as a flavouring and coloring agent for food, in perfumery, and for medicinal and religious purposes. The chemical constituents of saffron include zeaxanthin, crocin and crocetin (colors), picrocrocin (bitter principle) and safranal (flavor).

Zeaxanthin is one of the most common carotenoid alcohols found in nature. It is the pigment that gives saffron and many other plants their characteristic color. Zeaxanthin breaks down to form picrocrocin and safranal, which are in large part responsible for the taste and aroma of saffron.

> ***"Saffron can be cultivated in many areas. Economically, if each family had half a jerib or one jerib of land for saffron, we would be saved from poverty."***
> Bashir Ahmad Rashidi (head of the National Union of Saffron Growers of Afghanistan)[4]

Saffron as a Natural Product

90-95% of the crocus flowers used to produce saffron are grown in Iran.[6] It takes 150,000 crocus flowers and 40 hours of labor to manually extract enough stamens to yield 1 kilogram (kg) of saffron. After pistachio, saffron is Iran's most important non-petroleum export product. During harvest, each hectare devoted to saffron provides jobs for up to 270 people per day.[7] Good quality saffron sells from $2,000 to $10,000 US/kg or more.[8] Annual worldwide sales of saffron are an estimated $660 million US.[9] In 2009/2010, Iran's northeastern Khorasan Razavi province exported 57 tons of saffron worth $156.5 million US to 41 countries.[10] In 2014, Iranian saffron exports rose by 36%, despite international sanctions placed on the country.

Saffron cultivation in Kashmir, India forms an important sector for the livelihood security of more than 16,000 farm families located in 226 villages.[11] Herat Province of Afghanistan currently produces more than 90 percent of Afghanistan's saffron. 6,000 Herati farmers grow saffron and some 18 companies sell and export it abroad. It provides job opportunities to women since they perform 80% of the cultivation and processing work. It also represents an important source of income and an alternative to poppy-growing.[12]

Greek saffron is regarded as particularly high quality by chefs around the world. It is produced mainly in Kozani County, in a cooperative of 1000 member families employing 5000 people.[13] Saffron cultivation is important for both the growers, in terms of their farm income, and for the Greek agricultural economy, since all annual domestic production is exported.[14]

This crop also affects the livelihoods of around 1,200 farmers organized in Morocco's Taliouine Cooperative.[15] Their city of Taliouine produces more saffron than any other place in Africa. Every November, harvest time is also time for their saffron festival, and people from around the world come to watch and celebrate.

Biodiversity and Cultural Considerations

The saffron crocus has been cultivated for some 4,500 years, and was likely selected from a wild population precisely because of its vigour as a hybrid, visible in its impressive corolla and stamens. Flowering crops contribute to natural pest control management, promoting bee population and pollinator habitat; they increase the availability of pollen and nectar resources, and provide secondary benefits to the farms and surrounding landscapes. Contribution to a pollinator habitat enhances overall biodiversity and the ecosystem services it provides, as well as contributing to human cultural values and rural aesthetic.[16] Saffron is a plant with low water requirements and is perfectly adapted to a semi-arid environment that needs this kind of cash crop.

Medicinal preparations based on saffron have been found on Egyptian papyruses dating from the 16th century BC. Once considered a cure-all, saffron is still part of Chinese and Indian medicine. As a dye, saffron yields a luminous golden hue that was used by the Greeks and Chinese. Pages of important manuscripts were illuminated by a precious dye of saffron mixed with egg whites.[17] This crop is also strategically used as a tourist attraction in middle eastern countries.

Synthetic Biology Production

In 2010, Swiss-based synthetic biology company Evolva began working on a biosynthetic route to express saffron-derived genes in engineered microbes.[18] The goal was to build a novel metabolic pathway that instructs cells to produce key saffron compounds, which are then inserted into a microbial host for large-scale production in fermentation tanks (bioreactors). According to the company:

"Producing the key saffron components by fermentation has three main benefits. Firstly, it will allow saffron to be available at a much lower price than currently, which will both expand existing markets and open new ones. Secondly it will eliminate the many complexities involved in the current supply chain. Finally, by making each of the key components separately, it will enable the production of customized forms that are for example particularly rich in aroma, taste or colour and that can be adapted to specific food formulations and regional preferences."[19]

On March 30th 2016, Evolva published its financial results for 2015 and updates on coming projects. They announced, "We have successfully developed yeasts that make all three of saffron's key ingredients and entered scale up fermentation. Saffron extract and safranal have Flavor & Extract Manufacturers Association (FEMA) GRAS ('generally recognized as safe') status and we are preparing a GRAS submission to FEMA for our product. We provided samples of some of our saffron products to a number of potential customers during late 2015 and received very positive feedback regarding its aroma and options for additional applications. In line with our revised company focus, we aim to further develop saffron with a partner. This will likely move the launch to 2017 or later."[20]

Implications and the Future

In conversations with ETC Group, Evolva has claimed that their saffron will not so much replace existing saffron market as open up new uses for saffron as a flavour, since it will be affordable for use in processed snacks and other low-price products. There may be something to this; but if Evolva's saffron is sold as "natural" (because it is derived from fermentation) then it will be going head-to-head with current saffron markets.

Meanwhile the fortunes of botanical saffron on the world market are changing. Sanctions against Iran applied during the past decade have meant huge challenges for Iranian companies trying to export saffron to the US and Europe. However, in mid-January 2016 sanctions were lifted, allowing Iran to export freely to the US and elsewhere.[21] The future is looking brighter for Iranian saffron farmers, unless a new competitor has emerged in Evolva. In that case they will have to deal not with sanctions but a new first supplier of saffron at much a lower price.

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Sandalwood

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: Difficult to estimate because of illegal trade

Market Value: 15,000 tonnes of true sandalwood are produced annually[1] to meet market demand, commanding between $1,100 to 2,800 US/kg . The world market is worth up to $27 billion US

Uses: Perfume, cosmetics, religious uses and rituals

Syn Bio Companies: Evolva (Allylix), Isobionics, Firmenich

Hotspots: India, Indonesia, Australia

Still collected in the wild in: South Africa, Tanzania, Kenya, Pacific Islands

Also grown in: China, Sri Lanka, Thailand, Cambodia, Costa Rica are involved in the commercial cultivation and collection of East Indian sandalwood

Cultural Importance: Sandalwood use dates back four millennia. "Sandal" is derived from Chandana (Sanskrit) and was known as a wood and oil in Hindu, Buddhist, Muslim, Sufi and Zoroastrian religious traditions and medicines.

Biodiversity Considerations: Cultivation could help preserve wild sandalwood from extinction. This crop is well-suited for intercropping, as with grafted trees.[2]

Patents: WO 2010067309, WO 2014027118, WO 2010067309, WO 2015153501

Products: Santalol, Santalene

Method: Synthetically engineered yeast organisms

Commercialization: Isobionic's sandalwood is still under development.[3] Evolva's "santalol" fragrance is to be on the market in 2017. Firmenich launched its syn bio-derived Clearwood™ fragrance in 2014 which is primarily a patchouli replacement but imparts a "soft creaminess reminiscent of natural sandalwood."

Feedstock: Biomass

Brands, Identifiers: Clearwood™

Overview

Sandalwood refers to a fragrant oil derived from the heartwood of sandal trees. This essential oil has been used primarily in the fragrance industry; it is also used in medicine and aromatherapy. The wood is used for carving, especially religious objects; sawdust is used in incense. Documented uses date back four millennia. Legal plantations of sandalwood do exist and are increasing. However, the illegal cutting, smuggling and exploitation of sandalwood trees from wild forests is still highly problematic.

Status: Syn bio sandalwood is under development

R&D | Scale Up | Commercialization

Besides the pricey *Santalum album* (East Indian Sandalwood) there are also a range of cheaper faux-sandalwoods such as Amyris (West Indian sandalwood), found in Haiti and Dominican Republic.

At least two companies are focusing R&D efforts on producing a sandalwood oil fragrance using synthetic biology: Netherlands-based Isobionics, which spun off from DSM in 2008, and Swiss-based Evolva.

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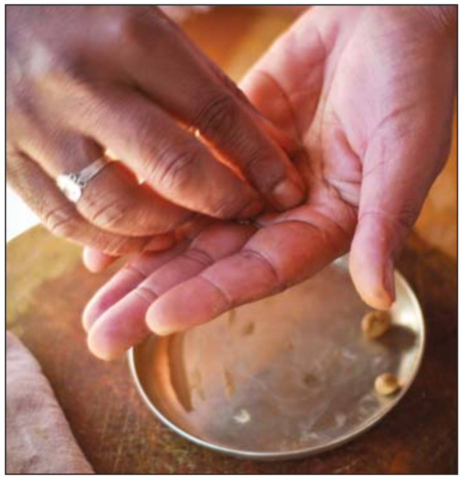
For more info on Synthetic Biology please visit the ETC Group website: **www.etcgroup.org/synbio**

Additionally, flavor and fragrance giant Firmenich holds patents on sandalwood biosynthesis and already markets a syn bio derived fragrance, Clearwood™, that has sandalwood notes. Syn bio sandalwood developers claim that their product will be a solution to the environmentally destructive cutting and smuggling of the tree. However, it will impact the option to scale up nascent ecologically and socially improved approaches to sandalwood growing, and will also negatively affect the production of Amyris and other cheaper alternatives.

What is Sandalwood?

Sandalwood refers to a fragrant oil derived from the heartwood of sandal trees. Produced via steam distillation, the oil has been used primarily in the fragrance industry; it is also used in medicine and aromatherapy. The *Santalum album* tree, commonly called East Indian sandalwood, produces the most prized sandalwood oil; the tree is native to parts of China, India, Indonesia and the Philippines and is semi-parasitic, meaning that it depends on the roots of other plants for nutrients.[4] Several other sandalwood species are found throughout the Pacific, including on Vanuatu (*Santalum austrocaledonicum*), Fiji (*Santalum yasi*) and Hawaii (*Santalum freycinetianum* and *Santalum paniculatum*).



Making sandalwood paste by hand
Photo (cc) Harsha K R

The odor profile of oil derived from *Santalum album* is complex, described by olfactory scientists as "lactonic, floral-woody, milky-urinous, animalic, somewhat musky."[5] An estimated 70 constituents contribute to the oil's scent, though *ß-santalol*, which accounts for about one quarter of the oil's weight, is considered to be "the main sandalwood odor constituent;"[6] *a-santalol* is another major constituent, though its odor is weak. *a-santalol* and *ß-santalol* are sesquiterpene alcohols.[7] So-called West Indian or "poor man's" sandalwood, derived from the wood of *Amyris balsamifera*, is not botanically related to East Indian Sandalwood and does not contain santalols, but is used as a lower-cost substitute in cosmetics, fragrances and soaps.

Sandalwood as a Natural Product

India used to be the largest producer of sandalwood oil, meeting over 80 percent of world demand. Over-exploitation and illegal traffic have caused production to decline drastically in recent years. It now attempts to grow more sandalwood both *in situ* and e*x-situ* by inter-plantation methods.[8]

The case of East Indian Sandalwood is particularly complex due to its vulnerability and history of exploitation. IUCN's Red List categorized *Santalum album* as vulnerable in 1998, noting that its status needed updating.[9] In India, where the government is considered the owner of all standing sandal trees, forest supplies are virtually non-existent due to poaching, fire and spike disease.[10] With increasing frequency, therefore, poachers are going after trees growing in urban areas.[11] As recently as April 2015, smugglers were caught with 77 kg of sandalwood logs illegally cut from trees growing within the city limits of Coimbatore, Tamil Nadu.[12]

By 2009, when *Forbes India* reported on the country's collapsing sandalwood oil trade, most of the family-owned distilleries in the oil-producing center of Kannauj (Uttar Pradesh) were already shuttered.[13] When Indonesia – formerly the world's largest supplier of raw sandalwood – banned the export of its sandalwood in the late 1970s, the result was inflated prices on the world market; exporting India's raw wood quickly became more lucrative than making oil, leading to the "widespread smuggling and mindless exploitation of sandalwood forests."[14] Australia then took over as the world's dominant sandalwood supplier – through its indigenous sandalwood species, *Santalum spicatum* – and began establishing its first plantations of *Santalum album*.

Now most of the world's East Indian sandalwood comes from plantations in Australia's tropical northwest region of the Ord River Valley.

Two companies control sandal tree plantations – a newly-formed private investment group called Santanol and Tropical Forestry Service (TFS).

Santanol's *Santalum album* plantations span 2,000 hectares; TFS has more than 9,000 hectares.[15] While profitable for the companies, the plantations have been declared a "disaster" for the region – sandal trees have supplanted food crops (melons, pumpkins, chick peas, bananas) and have taken land from indigenous communities.[16] In 2014, TFS completed its first commercial harvest of about 15,000 sandal trees[17] and almost the entire crop was purchased by Galderma, a Swiss pharmaceutical company wholly owned by Nestlé. They bought 470 kg of oil (worth $2.1 million US)[18] for use in an over-the-counter acne treatment in the USA.[19]

Besides true sandalwood, there are also a number of faux sandalwood species that are used by perfumers and product manufacturers to impart a cheaper sandalwood scent. An example is Amyris or 'West indian Sandalwood' – traditionally sourced from Haiti and the Dominican Republic. See box overleaf. There are already more than a dozen commercial sandalwood fragrance substitutes produced via conventional chemical synthesis – Givaudan Corporation sells three: Sandalore®, Sandela® and Brahmanol®.

Cultural and Biodiversity Considerations

Oil derived from *Santalum album* is problematic environmentally and socially. Cropwatch, a watchdog organization monitoring the natural aromatic products industry, notes that "the carbon footprint of sandalwood oil is particularly unacceptable with respect to climate change concerns, with excessive energy consumption occurring as a result of long distillation times."[20] Cropwatch further notes that buyers of sandalwood are "likely to be indirectly supporting gangland," since most oil is "either smuggled with or without the help of corrupt officials or otherwise illegally produced."[21]

The poaching of sandal trees standing in forests and cities is unacceptable, but plantations are not the solution if they take land, water and food away from local communities. Is there any other choice, then?

Amyris - West Indian Sandalwood from Haiti and Dominican republic

Amyris (Botanical name: *Amyris balsamifera*) is a small tree native to the Caribbean and Gulf of Mexico. Its fragrance is similar to sandalwood but it does not belong to the genus *Santalum*. Indigenous peoples of Haiti traditionally called amyris wood "candlewood" because of a high essential-oil content that caused it to burn quickly. The essential oil of amyris wood has a characteristic woody, sweet, smoky character.

Production areas for this wood are very hard to reach. The gathering and cutting in Haiti is done by indigenous farmers and takes a great deal of physical effort. According to Bernard P. Champon Sr., owner of the Haiti Essential Oil Company, in 2001, "Only the wood from trees that have died naturally is used. Collection of wood is carried out by 'speculators', who transport the material to the distilleries for sale."[22] Exports of Haitian amyris oil first began in 1943-44 according to an agricultural assessment of Haiti produced by USAID in 1987.[23] According to *Perfumer & Flavorist* magazine, throughout the first decade of the 21st century, Haiti's annual production of amyris oil was 60 metric tonnes (Note: This estimate was published in 2009, one year before the earthquake[24]). Though Haiti may still be distilling some amyris oil, the supply of native amyris wood is often described as depleted. Current reports suggest that all the *Amyris balsamifera* distilled in Haiti is coming from the Dominican Republic and is smuggled across the border.[25] Gilbert Assad of Arome et Essence d'Haïti, reported to ETC Group in April 2015 that, currently, amyris production is virtually non-existent in Haiti, due to the depleted supply of native wood but is still collected and distilled in Dominican Republic.[26] The introduction of a syn bio substitute for East Indian Sandalwood may conceivably also hit the market for faux sandalwoods such as Amyris with implications for these struggling pickers and distillers.

Red sandalwood seedpods   Photo (cc) Gail Hampshire

Do we have to choose between environmentally/socially destructive natural sandalwood oil, a chemical synthesis, and a syn bio oil produced by specially engineered microbes?

While the case of sandalwood oil dramatically illustrates the vulnerability and tragedy that can occur in natural product supply chains, it also illustrates the potential to support small producers as discussed in the case of Vanuatu, in Implications and the Future, ahead.

Synthetic Biology Production

At least two companies are focusing R&D efforts on producing a sandalwood oil fragrance using synthetic biology: Netherlands-based Isobionics, which spun off from DSM in 2008, has a syn bio derived sandalwood under development.[27] Swiss-based Evolva inherited a commercial development programme for syn bio sandalwood oil when it acquired Allylix Inc. in 2014.

Evolva expects to put its santalol fragrance on the market in 2017.[28] Swiss perfumer Firmenich SA launched its syn bio-derived Clearwood™ fragrance in 2014. While Firmenich primarily describes the trade-marked Clearwood™ as a "soft, clean version of patchouli,"[29] the company notes that when used as a fragrance building block, Clearwood™ imparts a "soft creaminess reminiscent of natural sandalwood."[30] Several patents have been granted or applied for related to the production of a-santalol and/or ß-santalol via engineered microorganisms.

In a patent on a syn bio method to produce ß-santalene as a precursor of ß-santalol (the major contributor to sandalwood scent), Firmenich makes the case for the value of creating an alternative to botanically-derived sandalwood oil:

"Due to over-exploitation of the natural resources, difficulties of cultivation, slow growth of the *Santalum* plants, the availability of sandalwood raw material has dramatically decreased during the past decades. Therefore, it would be an advantage to provide a source of ß-santalol, which is less subjected to fluctuations in availability and quality. A chemical synthesis of the sandalwood sesquiterpene constituents is so far not available… the present invention has the objective to produce ß-santalene while having little waste, a more energy and resource efficient process and while reducing dependency on fossil fuels."

Implications and the Future

Evolva and Firmenich are correct to argue that existing natural sandalwood oil production is problematic but that doesn't necessarily mean that synthetic biology should be the remedy. While the case of sandalwood oil dramatically illustrates the vulnerability and difficulties of always retaining natural products supply chains, it also illustrates the potential to support small producers: 2014 marked the first time that essential oil distilled from the heartwood of Vanuatu sandal trees was produced on Erromango in Republic of Vanuatu (formerly known as the New Hebrides in the South Pacific).[31]

Since the 19th century, Erromango's sandalwood had been bought, traded and stolen for processing in other countries. But in 2014, Pacific Provender Ltd, a family-owned business, established the first-ever sandalwood distillery on Erromango.[32] The "Erromangan Sandalwood and Essential Oil Association" represents 42 farmers; while the "Department of Forests of the Republic of Vanuatu" has trained and employed Ni-Vanatuan (indigenous) sandalwood growers to process the oil and produce value-added sandalwood products.[33]

Pacific Provender director Jeff Allen declared the project a success, reporting, "Everyone overseas who smelled our oil from Erromango loved it and wanted to buy more."[34] Even though Vanuatu's sandalwood oil is not from the traditionally most-prized species of sandal tree, that may be a price that has to be paid until (and if) India's sandal trees can recover and are protected. While every "livelihood project" – including the one on Vanuatu – must be scrutinized to assess its environmental credibility and social worth, small producers acting as stewards of native sandal trees should be supported in their efforts.

On the 14th of March 2015, a category 5 cyclone hit Erromango and sandalwood processing on the island came to a halt; but rebuilding is underway.[35] Would there have been enough incentive to restore the sandalwood-related livelihoods on Vanuatu if an inexpensive, syn bio-produced sandalwood fragrance – labeled "natural" – were already on the market? Other options, like those in Vanuatu, exist to access this fragrance, without encouraging illegal activities or devastating the livelihoods of those growing plantations of either sandalwood or similar other species.[36]

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Shea, Cocoa Butter & Other Cocoa Butter Equivalents (CBEs)

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: Cocoa: 5-6 million[1]
Shea Butter: 3 million African women[2]

Market Value: Cocoa: $6 billion US[3].
Cocoa butter equivalents: $600 million US[4] Including **Shea:** Between $90-$200 US million/year

Volume: Cocoa: 4.2 million tonnes (2014)[5]
Shea: 65,000 metric tonnes exported to Europe and North America annually (2015)[6]

Uses: Food products (edible fats, confectionery, bakery), animal feed, cosmetics

Syn Bio companies: TerraVia (previously Solazyme)

Hotspots: Cocoa: Cote d'Ivoire, Ghana, Indonesia[7], **Shea:** West Africa including Mali, Burkina Faso, Benin, Senegal, Ivory Coast, Ghana, Gambia, Nigeria

Also Grown In: Nigeria, Cameroon, Brazil, Ecuador, Mexico, Dominican Republic, Peru Other Butters: Indonesia, India, Brazil, Myanmar

Cultural Importance: Cocoa: Millennial tradition; a beverage of the Aztec gods, warriors and upper classes; was considered an invigorating and healthful drink also in Europe. **Shea:** Collected by women. Usage traditions date back to ancient Egypt.

Biodiversity Considerations: Cocoa: Shade crops provide habitat and food for plants and animals normally dependent upon tropical forest. **Shea:** Conservation of shea trees on fields and fallow land form part of a complex indigenous biodiverse farming system.

Overview

Cocoa butter and shea butter are vegetable fats used both for food and cosmetics applications. They are often described respectively as “cocoa butter” and “cocoa butter equivalents” (CBEs). CBEs include shea and other less common butters such as illipe, kokum, mowrah, murumuru, mango and palm butters. Cocoa butter is made from the beans of the cacao tree, grown across the tropics, while shea butter is made mostly from the oilseeds of the African shea tree.

Status: Syn bio shea / cocoa may be available 2016

R&D — Scale Up — Commercialization

At least 8-9 million smallholder famers and their families depend on growing and harvesting shea seeds and cacao beans, particularly in West and Sub-Saharan Africa.

Patents:
US20110293785A1: Food Compositions Comprising Tailored Oil

Products: Algal Butter

Method: Synthetically manipulated algae plants

Commercialization: 2016

Feedstock: Sugar cane or corn

Brands, Identifiers:
“AlgaWise algae butter”[8]

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

Cocoa butter use is particularly targeted towards the manufacture of chocolate, while Shea and other butters tend to either stretch food uses of cocoa butter or are even more commonly used in cosmetics as moisturizers.

In 2012, the synthetic biology firm Solazyme (later renamed TerraVia), announced that it had developed a new high-value "tailored oil" with a fatty acid composition very similar to cocoa butter.[10] One investor site brashly trumpeted: "Step aside cocoa farm, synthetic biology is on its way..." Solazyme, which genetically modifies sugar-fed algae to produce oils in giant vats, explained that its new algae butter is "ideally suited for a range of personal care products such as lotions, emollients and moisturizers."[11] In October 2015 Solazyme/TerraVia announced that AlgaWise butter will be on sale commercially in early 2016 and identified clearly that it was an alternative to shea noting that the algae butter "has a composition and functionality mirroring high value structuring fats such as shea stearin."[12]

"We can dislocate the production of that oil from a tropical climate to the middle of Iowa in winter and make an oil that is more nutritious and more stable." "It is truly revolutionary, that we can take what is a normal crop cycle and compress that into three days", Senior VP of Solazyme/TerraVia Mark Brooks.[9]

What are Shea, Cocoa Butter and Cocoa Butter Equivalents (CBE)?

Cocoa butter is derived from cocoa beans, grown by 5-6 million smallholder farmers in 30 tropical countries.[13] It is best known as the main ingredient in chocolate and the vast majority of cocoa butter is used for confectionery (i.e. food) and drink products. The proportion of cocoa butter that is used for non-edible uses (i.e. personal care products such as cosmetics, lotions) is very small: only 1-2% of total production, and that amount depends largely on the price of cocoa butter.[14] West Africa accounts for over 71% of all cocoa bean production, and Indonesia is also a major producer.

"Cocoa butter equivalents" (CBE), of which shea butter is one, are composed of vegetable fats derived from a variety of plant sources. CBEs are sourced from cheaper plant-derived vegetable fats, including: illipé (*Shorea stenoptera*), palm oil (*Elaeis guineensis, Elaeis olifera*), sal (*Shorea robusta*), shea (*Vitellaria paradoxa*), kokum gurgi (*Garcinia indica*), and mango kernel (*Mangifera indica*). The composition and price of CBEs depends on the current supply of many of these different plant-based oils.[15] The CBE market is especially used to "stretch" the cocoa butter supply–or to provide a cheaper raw material for lower-quality chocolate or for cosmetic products. The CBE market therefore varies from year to year depending on the price of cocoa butter, sometimes by 30% or more.[16]

Shea Butter is made from the seed of the fruit of the shea tree, *Vitellaria paradoxa* (syn. *Butyrospermum parkii, Butyrospermum paradoxum*). This tree is indigenous to a band of vegetation extending over 5,000 km from Senegal to Ethiopia and Uganda. It thrives in savanna areas where oil palm cannot grow due to low rainfall. Shea is not only overwhelmingly harvested by women (90%) but all stages from extraction to commercialization are controlled by women, making it an important crop for basic African livelihoods. Shea butter is a useful base for local pharmaceutical preparations, cosmetics and as a cocoa butter equivalent.[17]

Shea and Cocoa Butter as Natural Products

Cocoa farms are located in hot, rainy and tropical areas of Africa, Asia and Latin America, across a narrow belt falling within 10-20 degrees latitude of the equator. An estimated 4-5 million people in these often poor tropical areas depend on cocoa for their livelihoods.[18] Smallholder farmers account for 80-90% of world cocoa production. In Africa and Asia, a typical cocoa farm covers 2-4 hectares.[19]

The major producing countries for Shea are in West Africa: Mali, Burkina Faso, Benin, Senegal, Ivory Coast, Ghana, Gambia, Nigeria.[20] In recent decades, shea butter has become a valued ingredient in the finest natural cosmetics. The cosmetic and pharmaceutical industries consume an estimated 2-8,000 tonnes of shea butter each year, and this figure is expected to rise with growing demand in new markets.[21]

Processing of shea butter is often carried out by informal groups of women who pool their labour. Thus, in every producer country, rural women's groups and marketing associations have an important role in the shea butter industry. The UN Development Programme (UNDP) estimates that an average of three million women in Africa[22] and 16 million women[23] worldwide work directly or indirectly with shea butter. Moreover, it is estimated that 12% of poorest household total income comes from shea. A 2011 study by US Aid found that for every 1 MT shea nuts purchased from farmers at $220/MT, 128$ of additional household income is created in the regional economy.[24] Shea butter production offers jobs and higher income; improved family nutrition; better housing; and money to pay for school fees. Higher income in communities means improved access to potable water and construction of schools and medical centers.[25]

Cocoa butter prices normally determine shea butter prices for export values.[26] Like most tropical agricultural export commodities, cocoa and shea are subject to boom and bust cycles. Volatility in cocoa prices is due to many factors, including: extreme weather and climate change, pests and disease, political instability in producing countries, and corporate concentration in the cocoa value chain.

Shea and Cocoa Biodiversity and Cultural Considerations

Shade crops, such as cocoa and shea trees, provide habitat for plants and animals normally dependent upon tropical forest. It is also believed that shade plantations such as cacao may play a particularly critical conservation role for migratory organisms.[27]

The shea tree grows very slowly, yielding its first fruit harvest after 15 to 20 years. Mature trees are preserved during land clearance for farming and thus form part of the indigenous farming system, naturally maintaining a rich biodiversity and ecological preservation.[28]

Both cacao and shea have important cultural histories. Cocoa uses date back 4 millennia, to pre-Colombian cultures of Mesoamerica. It was made in a drink and was used as a monetary unit. A symbol of abundance, it was also used in religious rituals honoring the gods, in funerals and as a symbol of nobility and for soldiers during battles.[29] Ancient accounts tell of large caravans carrying clay jars of shea butter to queen Cleopatra of Egypt. African women have long used shea as a cosmetic, to ease child birth pains (northeast Ghana) and to cover newborn babies from head to toe to prevent infection (Gambia).[30]

Cocoa has become a focus of international consternation because of the discovery of fairly widespread use of child and slave labour in six of the 74 producing countries (all of them in West Africa). While industry promises, US legislation and UN targets are trying to end these practices by 2020, their efforts have so far produced disappointing results. Nonetheless, replacing cocoa butter altogether seems unlikely to be a relevant means of ending cocoa slavery. Arguably, undercutting prices with synthetic alternatives could have the effect of worsening prices and labour conditions, just as much as possibly benefitting them. Overall, in terms of this being a profitable and culturally important product that benefits poor families, cocoa is still a desirable crop.[31]

Synthetic Biology Production

California-based TerraVia (formerly Solazyme) develops engineered microalgae (pond scum) which secrete "tailored" oils (altered algae oil that mimics other vegetable oil profiles) for use in chemicals, foods, fuels and personal care/health products. Solazyme/TerraVia believes the food and cosmetics business provide tremendous opportunities for these products to develop into large and profitable entities.[32]

In 2012, TerraVia announced that it had developed a new high-value "tailored oil" with a fatty acid composition very similar to cocoa butter.[33] The company explained that its new algae butter is "ideally suited for a range of personal care products such as lotions, emollients and moisturizers."[34] One investor site brashly trumpeted: "Step aside cocoa farm, synthetic biology is on its way..." In 2014 CEO Jonathan Wolfson reiterated that "Looking forward, a number of the high-value oils we're working on have important application potential in nutrition, and these include [...] cocoa butter equivalents."[35] Then, in 2015, TerraVia announced that its "AlgaWise Butter" was going through the GRAS (Generally Recognized As Safe) process and should be available on the US market in early 2016.[36] They identified more clearly that it mimics shea stearin – which is the fatty part of shea butter and that as such it will also be incorporated into foods. This AlgaWise Butter is currently being tested by manufacturers in spreads, bakery and confectionary applications, and could be used in any type of food where the fats are solid at room temperature. Solazyme has confirmed that its high oleic oil and structured fats (butter) are genetically engineered in order to make a precisely tailored oil with unique functionality.[37]

AlgaWise Butter Customers may include Hormel, Utz, Enjoy Life Foods, So Delicious, Soylent and Follow Your Heart. Manufacturers are likely to be allowed to describe it as "algal butter" on the ingredients list, according to Mark Brooks, senior vice-president. "I don't think we are precluded from calling it algae butter, just as you are allowed to say 'cocoa butter' and 'shea butter', which are not dairy-derived either," Brooks told Food Navigator-USA in November 2015.[38]

This syn bio butter is part of a line of oils for cooking, baking and dressing that TerraVia is producing in a partnership with grain giant Bunge. They include AlgaWise Algae Oil and a consumer brand called Thrive Algae Oil already on the market. Bunge is in charge of marketing the oils and butter, and handles the oil processing and supply chain aspects of commercialization. Manufacturing takes place at the joint venture's facility in São Paulo, Brazil, that is adjacent to Bunge's Moema sugarcane mill, the feedstock for the syn bio algae.[39]

Implications for the Future

For quality reasons, cocoa butter equivalents do not normally impact the chocolate market very much, so there is lower potential for a biosynthesized cocoa butter alternative to impact that larger part of the cocoa market that goes to chocolate makers. Demand for cocoa beans currently outpaces supply, and corporate cocoa giants are currently investing millions of dollars in new cocoa-grinding operations and processing facilities. They would probably not be doing so if they were looking towards using a cheaper, biosynthesized cocoa butter equivalent in the near future. However, if TerraVia is able to offer low-cost and high-yields of their algal cocoa butter equivalent, then it might prove significantly disruptive to the parallel markets for cocoa butter equivalents such as shea.

Observers have speculated that Solazyme's technology will enable the "de-regionalization" of cocoa butter equivalent production, eliminating constraints associated with the sourcing of natural cocoa beans from tropical countries: volatile prices, unpredictable supplies, long-distance shipping and geopolitical instability.[40] In an interview given on the occasion of the IFT 2015 show in Chicago in the summer, TerraVia Senior VP Mark Brooks touts this disruption as a benefit: "It is truly revolutionary, that we can take what is a normal crop cycle and compress that into three days... We can dislocate the production of that oil from a tropical climate to the middle of Iowa in winter and make an oil that is more nutritious and more stable."[41]

However, moving production from the land to the vats could have wide-reaching negative effects on the lands and the 5-6 million farmers who produce cocoa beans, and especially on the 16 million women involved in the shea butter industry worldwide.[42] It could also displace or disrupt markets and farming communities around the world for other tropical oils and butter equivalents such as coconut oil, palm oil, palm kernel oil, shea butter and other smaller sources of butter such as illipe, kokum, mowrah and murumuru which are typically used as cocoa butter equivalents.

Beyond Shea: Other Cocoa Butter Equivalents (CBE)

Tengkawang nuts

In the food and cosmetic industry, some butters are considered substitutes for cocoa butter - the most important for Western cosmetics are illipe, mowrah, kokum, murumuru and mango butters. Others include: sal, palm, tucuma, cupuacu butters. Illipe butter is considered the best substitute for cocoa butter because of its similar melting points and fatty acid profiles. Mowrah butter is used as a substitute for shea butter. Illipe and mowrah butter are often sold as the "other butters" on the ingredient list (they can also be called Borneo tallow or Tengkaway).

Illipe (or Tengkawang) butter: Derived from seeds of *Shorea stenoptera*, an Asian tree that is native to Borneo forests. The Borneo Dayaks (indigenous to the area) have been making a butter from Illipe nuts for countless centuries. Today, Indonesia is the main producer and exporter of the tree's tengkawang nuts. Almost all production is exported and account for a value of roughly $7.75 million US[43].

Mowrah: The fruit of the mahua *(Madhuca longifolia)* tree grown in India. Used for both edible (chocolate) and cosmetic applications, it is also utilized in the manufacturing of laundry soaps and lubricants as well as creams, lotions, and balms.

Murumuru butter: The *Astrocaryum murumuru* palm grows in Brazil and around the Amazon and is one of the dominant trees in this region. It is used in small amounts in shampoos (0.5% to 1%) and formulas for conditioners, creams, soaps, lipsticks and deodorants.

Sal butter: In India, *Shorea robusta* or sal forests occur over a wide area: 114,379 sq. km. Production data are unknown as most is consumed domestically.

Kokum butter: Fruit of the *Garcinia Indica* tree of India, it is used in cosmetics, especially lip balms; little market information is available..

Cupuacu butter: *Theobroma grandiflorium* is related to cacao and is native to the northern Amazon.

Palm butter: Comes from the fruit the African oil palm *Elaeis guineensis.* It Is widely used in food and cosmetics in Africa.

Mango butter: Used in baby creams, sun care balms, hair products, and other moisturizing products. India has 57% of total production. Myanmar and southern Asia also make it.

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Squalane (Olive)

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: 30 million people make living from olive sector[1]

Market Value: $93 million, $141 million US by 2019

Volume: 2,500 metric tonnes / year

Uses: Cosmetics

Syn Bio Companies: Amyris

Hotspots: Spain, Greece, Italy and North Africa (Morroco, Tunisia)

Also grown in: France, Syria, Turkey

Cultural Importance: Olive-growing and use are closely woven into Mediterranean culture and Judeo-Christian religion.

Biodiversity Benefits: Older olive groves exhibit high biodiversity benefits and integrate with livestock farming. Newer intensive olive plantations raise agrochemical and erosion issues that can be mitigated with organic production.

Patents: US20120040396A1, WO2012024186A1, US20100267971A1, WO2010115097A3

Products: Cosmetics (Make-up removing cloths, face oil, cleansing oil, body moisturizer, hand cleaner)

Method: Synthetically engineered yeast

Commercialization: On the market

Feedstock: Sugarcane

Brands, Identifiers: Neossance™ Squalane, Biossance™ products[2]: "The Refresher", "The Nourisher", "The Purifier", "The Revitalizer", Peter Thomas Roth's "Oilless Oil 100% Purified Squalane", Elizabeth Arden, among others. "Muck Daddy" hand cleaner degreaser

Overview

Squalane is a high-end, "oil-free" moisturizing ingredient, found in nature and used in many cosmetics. Until recently, it was extracted primarily from the livers of deep sea sharks. However, following demands from civil society campaigns, deep-sea shark harvesting became prohibited in many parts of the world and many brands removed shark-derived squalane from their cosmetics in favor of renewable plant-based sources.[3] Squalane is therefore today derived largely from botanical sources, mostly olive oil. Since 2010, leading synthetic biology firm Amyris Biotechnologies has been marketing its so-called "sugar-derived" squalane as Neossance™.[4] The Amyris squalane is produced by bioengineered yeast fed on Brazilian sugarcane, and has gained a significant hold in the cosmetics market, used today by a wide variety of brands. It is also sold by Amyris' in-house cosmetics brand Biossance™.

Status: Syn bio squalane is already on the market

R&D — Scale Up — Commercialization

What is Squalane?

Squalane is a high-end moisturizing ingredient used in many cosmetics. It is naturally found throughout the plant and animal kingdoms, even in human skin. Squalene (the shark-derived version of squalane) was discovered in 1906 by the Japanese oils and fats expert Dr. Mitsumaru Tsujimoto, when he investigated the part of shark liver oil that would not saponify (turn into soap)[5].

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He named the substance after the shark family it came from (*Squalidae*); however it was later found to also exist in smaller quantities in other animal and vegetable sources, including amaranth and wheat germ. Besides moisturizing properties, squalane is a hydrocarbon and a triterpene, and is a natural and vital part of the synthesis of all plant and animal sterols, including cholesterol, steroid hormones, and vitamin D in the human body. Squalane has recently been used as an immunologic adjuvant in vaccines and as an antioxidant. Research suggests that squalane, as a part of the Mediterranean diet, may be a chemopreventive substance protecting people from cancer.

Squalane as a Natural Product

Until recently, Squalane was commercially extracted from the livers of deep sea sharks. Livers of an estimated 3,000 sharks are required to produce just under 1 ton of squalane. Up to 2.7 million deep-sea sharks a year were thus killed to meet the global demand for squalane in the cosmetic industry alone.[6]

More recently, the majority of squalane on the market has been derived from botanical sources including rice bran, wheat germ, amaranth seeds and most importantly, olives.

In 2008, following campaigns by civil society, L'Oreal and Unilever announced that they would remove shark squalane from their cosmetic brands in favor of renewable plant-based sources; so deep-sea trawlers gave way to Mediterranean and North African farmers and exporters. Today, refined olive oil as the primary source. The first compression of olive oil contains about 400-450 mg per 100g of squalane, while refined oil contains about 25% less. In some cases, premium quality olive oil contains concentrations of up to 700 mg per 100g. Amaranth may also become an important vegetable source of squalane in time since it has higher concentrations than olive. The cosmetics industry is already the biggest consumer of the amaranth seed oil market buying a market share of above 60% in 2013.[7]

Global squalane production was 2,500 metric tonnes (MT) in 2013. Of that, 1,050 MT was produced from olive oil, 1,000 MT from shark liver, and 450 MT from Amyris' synthetic biology organisms. At current prices, the market represents $93 million US in sales. A recent press release estimated the squalane market will be worth more than $141 million US by 2019.[8] Global consumption of squalane is expected to be 4,028 tons by 2019. Amyris has been the most active company in the squalane market in recent years.[9]

Global olive oil production, to which squalane supply is now linked, is currently 2.9 million tonnes of which just over 2 million is produced within the European Union's Mediterranen region. Spain is the leading olive oil manufacturer at 1.3 million tonnes, along with Greece and Italy. Spain produces 46% of the world'ss olive oil, with this oil accounting for €1.8 billion of Spanish exports in 2011, making it the country's third most important agricultural commodity after wine and pork. Greece has 531,000 olive oil farms and Italy has more than one million farms. Other major producers are Syria, Turkey, Tunisia and Morocco.[10] Moroccan olive production is in a phase of notably rapid growth. The country doubled its olive oil production in recent years to 1.5 million tons, reducing unemployment for women in particular, by creating over 300 000 permanent jobs.[11]

Biodiversity and Cultural Considerations

While large scale extraction of squalane from shark livers has been roundly condemned by marine protection organizations, the now more common sourcing of squalane from olive farms would seem to be an overall beneficial move for both agroecological landscapes and Mediterranean farming communities. When squalane is sourced from olive oil, it is actually a by-product of the refining process, and is considered a useful component of olive mill wastes.[12] Squalane is found in relatively high concentrations in olive-oil residues after the last production steps (deodorization), and is also a waste product of the refineries. As such, olive squalane production does not necessarily compete with food, or drive additional land use demands, while it does add to the value of the olive harvest.

Olive production in the Mediterranean region occurs in orchard systems with trees that may be many hundreds of years old. Older orchards, while less efficient, are recognized for their high biodiversity benefits - offering shade and habitat for owls and other birds and are integrated with livestock grazing (particularly sheep and goats), removing need for herbicide or fertilizers. Olive groves traditionally have low water needs and can support a high diversity of plant species. For example, there are reports of as many as 100 species of plant per hectare in the ground flora and over 500 species in the olive area of Cordoba province. Another survey refers to 120 plant species, 70 vertebrates and 160 invertebrates associated with olive plantations.[13] More modern, densely stocked and intensive olive plantations do raise concerns associated with use of agrochemicals as well as soil erosion. However, even in such intensive systems, organic production avoiding pesticides is becoming increasingly common. Older, traditional olive groves rarely require chemical applications.

Olive growing, olive groves and use of olive oil have been woven into the cultures of Mediterranean societies for thousands of years. The long life of olive trees have led to them being revered as signs of fertility and vitality, of purity and of culture. The ancient Greeks named their most important city after the goddess Athena because she gave the olive tree as a gift. Judeo-Christian religious tradition has many references to the olive and olive groves. The symbol of the olive branch, originally from the bible, became a universal sign of peace now incorporated into the flag of the United Nations.

Synthetic Biology Production

In February 2010, the California-based synthetic biology company Amyris entered a partnership with Soliance, a provider of ingredients to the French cosmetic industry, to sell large quantities of its Neossance™ squalane to the cosmetic industry.[14]

In 2011, Amyris also entered into a multiyear agreement to provide "several hundred tons" of squalane to Nikko Chemicals Co. Ltd. for distribution in the Japanese market.[15] In 2015, Amyris announced a further partnership with Squalan Natural Health, a privately held personal care products company based in the Netherlands, for the production and marketing of "Neossance Squalane." Finally, on February 18, 2016, Amyris launched its own in-house brand Biossance™ a collection of skin care products using its squalane and the closely related compound hemisqualane. This product line includes moisturizers, cleansing oils, make-up removing cloths, etc. They are being commercialized by the Home Shopping Network, an "interactive, multi-channel" fashion and beauty company. Another of Amyris' own product lines, "Muck Daddy," commercializes a moisturizing hand cleaner degreaser based on squalane.[16]

Amyris had previously engineered the metabolic pathway of yeast to produce a molecule called farnesene, an essential building block for a wide range of chemical products, including squalane. Their production of Neossance Squalane and hemisqualane builds on this core technology. Since Amyris bioengineered yeast feeds on Brazilian sugarcane, the company and brands that use it claim that Neossance squalane is "sugar-derived" or "sugar squalane," with no mention of synthetic biology-created microorganisms. Amyris has presented Neossance as an ethical alternative to shark squalane, with company PR presenting their product as a synthetic biology breakthrough, saving the lives of thousands of sharks. The claim fails to adequately take into account the existing plant-based production of squalane via olives and other plants. They do, however, claim Neossance as a "sustainable" product, arguing that sugarcane production in Brazil is a far more efficient use of land than olive oil.[17] Besides the numerous heavy environmental and social costs that do accompany growing sugarcane in Brazil, this analysis overlooks the fact that when olive squalane is produced from waste streams its land impact is negligible.

Continually commercialized as "100% plant-based," or "made from plant sugars," Amyris' squalane has successfully infiltrated the cosmetic market as a new renewable, responsible and healthy alternative. Brands such as Clarins, Revlon, The Face Shop, Aveeno, L'OCCITANE, Elizabeth Arden and Thomas Peter Roth presently commercialize at least one of Amyris' syn bio ingredients.[18] Despite being from a clearly unnatural bioengineered source, Amyris market their syn bio squalane with "green" and "natural" branding. Neossance is certified by ECOCERT "in accordance with the Natural and Organic Cosmetics standards"[19] and has the "Natural Seal" certification from the Natural Products Association.[20] Additionally, the Environmental Working Group (EWG), a nonprofit who advocates for environmental health and nontoxic products, has just granted its "EWG VERIFIED™" seal to the Biossance™ moisturizer "The Revitalizer" . The EWG VERIFIED™ standard is said to have been "created to educate consumers, empower them to make smart choices and to change the market." Their "skin deep database" has "strict guidelines of criteria" in order to "rate thousands of products to inform and educate consumers on what is in their products and why it matters.[21] Amyris even claims that their squalane is "GMO-free" because the squalene itself contains no engineered DNA though it is produced by a GMO yeast.[22] Biossance's advertising plays on the fact that squalane is naturally found in the human body and focuses on women's empowerment through beauty. Again, the unnatural, industrial source of the ingredient is not disclosed.

Neossance's real advantage, beyond the marketing hype, might be its cost. While squalane from olive oil is 30% more expensive than that derived from sharks (8-12 euros/kg more expensive)[23], Amyris' biosynthetic squalane may be a cheaper non-shark option than olive squalane.

Implications and the Future:

Neossance Squalane has been an important beachhead product for Amyris and for the use of syn bio-derived ingredients in cosmetics. Its appeal however rests on a mix of cost savings for manufacturers and misleading marketing in what consumers are told. Neossance™ may be cutting a little into the shark squalane market, but it is more significantly undercutting production of squalane from olives and other plans, which provide added value to olive producers and are more genuinely sustainable and 'natural.'

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Stevia

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: Tens of thousands.

Market Value: For stevia leaves and powders, etc.: $347 million in 2014, growing rapidly to $565.2 million by 2020[1]; The market for stevia-sweetened goods (drinks, candies, etc.): $8-11 billion (2015)[2]

Volume: Stevia consumption expected to reach 8,506.9 tonnes by the end of 2020[3]

Uses: Non-caloric sweetener

Syn Bio Companies: Evolva, Cargill, Stevia First, DSM

Hotspots: China (80%), Paraguay (3%), USA, Argentina, Colombia, Kenya,

Also Grown In: India, Vietnam, Brazil, South Korea, Taiwan

Cultural Importance: Traditional food, medicinal uses by indigenous Guarani people, highly prized in Paraguay; today seen as possible help in obesity epidemic

Biodiversity Considerations: Low land use, can be grown without agrochemicals, low CO_2 footprint

Quality issues: Syn Bio firms are not producing true stevia but only mimics of single "rebaudioside" compounds usually found in small quantities within the natural leaf. In some European states it is prohibited to represent these purified single compounds as "stevia."

Products: Steviol glycosides (rebaudiosides) are widely used as sweeteners in dairy food products, bakery products, dietary supplements, confectionery, table top sweeteners, beverages, packaged food products, snacks.

Method: Synthetically engineered yeast

Commercialization: 2017

Feedstock: Corn syrup, sugar

Brands, Identifiers: Eversweet

Overview

Stevia (*Stevia rebaudiana*), a leafy plant characterized by its sweet taste, has its origins as a traditional food and medicinal ingredient of indigenous Guarani peoples in Paraguay and Brazil. Because of its rapidly-growing use as a zero-calorie natural sweetener, global demand for stevia is experiencing explosive growth. The revenue from stevia-sweetened goods was pegged at between $8-11 billion US in 2015.[4]

Status: Syn bio stevia will be launched in 2017

R&D — Scale Up — Commercialization

Ingredient companies are now isolating the key sweetening compounds in stevia, steviol glycosides (sugars) known as rebaudiosides, and producing them individually for use in mainstream market brands. Some of these compounds are thought to have up to 350 times the sweetness of sugar and are being widely incorporated into leading soft drinks such as Coca Cola Life and Pepsi True as well as baked goods, candies, etc.

At least three commercial companies are working to commercialize steviol glycosides created through synthetic biology. Grain giant Cargill has teamed up with synthetic biology leader Evolva SA to engineer yeast to create rebaudiosides.

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Their syn bio sweetener, named Eversweet, is ready for market but has been delayed until 2017 while optimizing production and awaiting regulatory approvals. Cargill is already one of the world's largest players in stevia. Stevia First of California have also developed steviol glycoside ingredients produced from a similar fermentation process. A third company, the multibillion-dollar Dutch chemical producer DSM, is also scaling up its "fermented" syn bio stevia product.

What is Stevia?

Stevia is a natural sweetener for food and beverages derived from Stevia rebaudiana, a leafy plant originating in the border region of Paraguay and Brazil in South America. Characterized by its sweet taste, it is claimed to be a zero-calorie alternative to sugar. The use of stevia originates with indigenous Guarani peoples, who use whole stevia leaves medicinally as well as to sweeten Yerba mate and other foods. While whole stevia is still used, commercial use has focused on a range of single sugary compounds extracted from the stevia leaf, known as Steviol glycosides. These include Reb A (Rebaudioside A), Reb C, Reb F, Reb M, Reb D, Reb X and Stevioside. These compounds can have up to 350 times the sweetness of sugar. Some purified rebaudiosides (e.g. Reb A) have been approved for use in food products in major markets such as the US and Europe, even though the use of whole stevia leaf for food is restricted because regulators claim they have 'inadequate toxicological information' to determine safety. In response to growing concerns and regulatory action to counter the global obesity epidemic, the food and soft drink industry in particular is embracing use of these intensely sweet rebaudioside extracts as a means to cut down sugar in processed foods. Coca Cola for example uses stevia extracts in 45 different products, including its high-profile "Coke Life," sold in 15 different countries. According to business research compiler Future Market Insights, the global stevia ingredient market could reach $565.2 million US by 2020, amounting to 15% of the global sweetener market, and revenue from stevia-sweetened goods was pegged at between $8-11 billion US in 2015.[5]

According to the Global Stevia Institute, more than 5,000 food and drink products now contain steviol glycosides.[6] In 2009 the World Health Organization estimated that steviol glycosides have the potential to replace 20-30% of all dietary sweeteners in the coming years.[7]

Stevia as a Natural Product

Stevia originated as a wild plant in Paraguay and the border region with Brazil; however, wild stevia is now virtually extinct.[8] Today all stevia leaf comes from stevia farms. It is most widely cultivated in China, Paraguay, Argentina, Kenya and the United States, but is also being established in Colombia, India, Vietnam, South Korea, Taiwan and Brazil. Global cultivation in 2010 was estimated at 50,000 acres. Over 80% of stevia is grown in China and only 3% in its place of origin, Paraguay.

Stevia growing was introduced to Kenya by Malaysian Company PureCircle Inc. and acreage has rapidly grown since. PureCircle buys all 10,000 tonnes of Kenyan stevia leaf from 5-6,000 Kenyan farmers based in eleven counties and hopes to scale up Kenyan growing of this crop to 10,000 farmers. When ETC Group spoke with Kenyan stevia farmers in Kericho county, we learned they typically devoted a quarter to half an acre of their small farm to stevia. However, the comparatively high prices for growing stevia were leading them to uproot their tea crops to plant stevia, and there was a lot of excitement and pride in the new cash crop. The leaves can be harvested every 2-3 months (by hand) and bushes last for five years before quality drops.[9]

Most of the world's stevia leaf is chemically processed into steviol glycosides by a handful of companies, principally PureCircle and Cargill. The most widely used glycoside is Reb A, which also has the highest concentration in stevia leaves. However, Reb A suffers from a slightly bitter metallic aftertaste; so its use in soft drinks and other applications needs to be supplemented by sugar. Subsequently stevia companies have been trying to commercialize other glycosides found in much smaller quantities in natural stevia, such as Reb X, Reb D and Reb M.

Because of the smaller quantities per leaf, larger harvests are required to extract commercially useful amounts. US and European regulators have approved several specific steviol glycosides for food consumption, including Reb A, Reb C, Reb D, Reb F, Reb M and Reb X. Indigenous advocates and some natural health practitioners point out that it is misleading to call these purified rebaudioside ingredients "stevia," "natural," or to use images of the leaf. In some countries (eg. Germany, Switzerland and Austria) national guidelines prohibit misrepresenting chemically purified rebaudiosides in these ways.[10]

Biodiversity and Cultural Considerations

Much of the marketing around commercial stevia stresses its origin from indigenous communities. Stevia was originally used as a sweetener and medicine by the Kaiowa Guarani in Brazil and the Pai Tavytera Guarani communities in Paraguay, who refer to it as Ka'a He'ê (meaning "sweet herb"). Paraguay in particular regards stevia as a national treasure. The Pay Tavytera have a small population of 15,000 who now have access to only a small part of their traditional territory. Despite being hunters, fishers and gatherers, they are increasingly dependent on small scale agriculture and paid work on cattle ranches. The Brazilian Kaiowa Guarani have dwindled to 46,000 people who have also lost most of their territory and are now largely living precarious lives on small reserves surrounded by sugarcane plantations and cattle farms, where many work in slave-like condition.[11] Many indigenous advocates and others have pointed to the current commercial boom in steviol glycosides as a classic case of biopiracy, where the original stewards of stevia are granted absolutely no benefits from the ever larger corporate profits flowing from this plant in the global marketplace.

In biodiversity terms, stevia appears to be an ecologically benign crop. Stevia farmers that ETC Group interviewed in Kenya stressed that the plant does not require agrochemicals. The Kenyan farmers apply organic manure and weed by hand.[12] The Global Stevia Institute claims that stevia is a land-sparing crop, since high production can be attained on small bits of land. Significantly, it may also be a much less carbon intensive crop than other sweeteners like sugar cane, and including the sugary feedstocks like corn syrup used for producing syn bio steviol glycosides. In a 2013 study, the carbon footprint of natural stevia was shown to be 79% lower than high fructose corn syrup (HFCS), 55% lower than beet sugar, and 29% lower than cane sugar, based on industry production standards.[13] A similar study in 2012 claimed that "high purity stevia sweeteners have a carbon footprint that is as much as 82% lower and a water footprint that is as much as 97% lower than other publicly available sweetener benchmarks".[14]

Synthetic Biology Production

There has been intense interest and competition to commercialize the synthetic biology production of steviol glycosides, driven by two key factors. Firstly, synthesizing some of the rarer glycosides inside engineered microbes (ie. Reb X, Reb M and Reb D) holds out the possibility of being able to cheaply mass produce a steviol glycoside that does not have the bitter aftertaste of the more abundant Reb A. Even more exciting for the industry is the prospect that in many jurisdictions, the products of synthetic biology can be legally described and labelled as "natural" (because fermentation is legally considered a natural process). This means that such syn bio steviol glycosides could be very quietly incorporated into profitable natural products markets.

Two of the three companies working on syn bio stevia are large firms racing for commercialization. Cargill and Evolva's joint venture to commercialize Reb M and Reb D has been consistently ahead of schedule. They established a pilot production plant in Blair, Nebraska and in October 2015 they unveiled their commercial sweetener, dubbed "Eversweet," at a large ingredients conference in Las Vegas. They had expected it to enter the market in 2016. However, Evolva now says that Eversweet's entry to the US market will be later as they are attempting to bring costs down and are still waiting for the substance to recieve USDA approval as GRAS ("Generally Recognized As Safe")[15]

Cargill's existing stevia line ("Truvia") and its relationship with Coca Cola, puts both corporate giants in a position to realize high profits, particularly if Coca Cola chooses to substitute real stevia for Eversweet in their "Coke Life" product. Meanwhile, DSM , a large Dutch chemical and ingredients producer, had announced in 2014 that they were seeking USDA GRAS approval for another syn bio stevia and intended to launch their syn bio stevia product by the end of 2015.[16] DSM's syn bio yeast produces Reb A, the bitter one. It is expected that both DSM and Cargill/Evolva will seek to market their syn bio steviol glycosides as "natural" ingredients, even though they come from an almost unimaginably extreme genetic engineering process. "We are getting a yeast to produce stevia much as a yeast might produce alcohol, something that is impossible in the natural world," says Greg Kesels, Regional President of Food Ingredients for DSM. Without missing a beat, he concludes "...it is exactly the same product as you might find in nature." Other companies in the US are also getting onboard this train, like Stevia First of California.[17]

Implications for the Future

Syn bio steviol glycosides are poised over the next few years to be one of the largest volume and most commercially important synthesized ingredients to enter a vast amount of food and beverages. Whether DSM or Evolva/Cargill commercialize first, the switch in human consumption of a syn bio-derived sweetener will probably not be advertised. Consumers will continue to be told that they are being offered a "natural" product. Already some companies producing leaf stevia have been speaking out against this coming deception. In 2014, Pure Circle Stevia said that their polling data showing that consumers expect natural stevia to come from a plant[18]; and in 2015, a number of stevia trade associations openly attacked the new syn bio "fermentation" stevias as likely to damage the industry's reputation:

Euromonitor analyst Simone Baroke warns: "Stevia's already wobbly status as the only "natural" low-calorie sweetener is about to be thrown into even greater jeopardy... The mere fact that a product is based on an innocuous raw material is not sufficient to pull the 'natural' wool over consumers' eyes." The European Stevia Association (EUSTAS) concurred: "Of course this will damage the natural reputation of stevia even if (in Europe) stevia extracts are not allowed to be labelled as "natural" but from "natural origin", board member Monica Lorenzo also told *FoodNavigator*, adding, "The expectation of consumers is to get a natural product, and this is no longer the case when produced through fermentation. Furthermore, this is not a fermentation process that could be considered as natural (like for cheese, wine, beer, yoghurts...) but a fermentation process that uses genetically modified yeast, so a type of production that doesn't exist in nature."[19]

At the same time, cultivation of true leaf stevia is ramping up, providing much-needed income for small farmers, especially in Kenya. Farmers, in many cases, who also grow a variety of food crops, are effective stewards of local biodiversity. However, if companies like Evolva can scale up production of synthetic yeast (and steviol glycosides), the benefits of the growing market for stevia may go to the shareholders of Cargill and Evolva instead of small farmers. Instead of sustainable cultivation, production based on synthetic organisms could drive demand for sugar, a crop associated with deforestation and human rights abuses, as well as high CO_2 emissions.

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Vanilla

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: 200,000

Market Value: $150 million US (beans)
$650 million US (beans and synthetic)

Uses: Flavour, fragrance

Syn Bio companies: Evolva, International Flavors and Fragrances (IFF)

Hotspots: Madagascar, Comoros, Réunion, Uganda, Mexico, Tahiti

Also Grown In: Indonesia, China, Democratic Republic of Congo, Tanzania, French Polynesia, Malawi, Tonga, Turkey and India

Cultural Importance: Used in Mexico since at least the 1400s as flavouring, tribute, currency: the Fruit of the Gods. The most popular flavouring in the world today, used in countless foods, beverages, cosmetics, household products.

Biodiversity Considerations: Agroforestry cultivation method protects forests and biodiversity; prevents deforestation because it is generally cropped in the forests.

Quality Concerns: Only a few of the hundreds of chemical components in true vanilla are being synthesized in the synthetic biology version – primarily the compound vanillin. Despite being synthetically produced by bioengineered yeast Evolva and IFF intend to misrepresent their product to consumers as a 'natural flavour'.

Patents: WO 2013022881

Products: "Always Vanilla"

Method: Synthetically engineered yeast

Commercialization: Already on market

Overview

Natural vanilla is derived from the cured seed pod of the vanilla orchid, which grows as a vine in tropical climates. Vanilla production is labour intensive, requiring cultivators to hand-pollinate vines dispersed in forested areas. The pods take about five months to mature, after which they are collected by hand and cured. An estimated 200,000 people are involved in the global annual production of cured vanilla beans. Madagascar, Comoros and Réunion historically account for around three quarters of the world's vanilla bean production. At the consumer end, natural vanilla sells for thousands of dollars per kilogram, while synthetic "vanillin" sells for about ten times less.

Status: Syn bio vanillin is already on the market

R&D — Scale Up — Commercialization

Evolva, a Switzerland-based synthetic biology company, has partnered with US industry giant International Flavors & Fragrances (IFF) to engineer metabolic pathways in microbes to produce key flavor compounds found in vanilla. Evolva and IFF commercialized a bio-synthesized vanillin flavor in 2014 which is now sold as part of IFF's "Always Vanilla" line.[1]

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

What is Vanilla?

Vanilla (Spanish for "little pod") is both a plant and the flavouring derived from it. Its origins are in Mexico, and because of a specific local pollinator, could not be grown elsewhere until the 19th century. A slave, Edmond Albius living on the island of Reunion in the Indian Ocean, discovered how to easily hand-pollinate it. Since then, the production of the species *Vanilla planifolia* is the most common.[2] This is known as Bourbon or Madagascar Vanilla and is produced still in the area of Madagascar and Reunion, as well as in Indonesia, China, Mexico, Uganda and other tropical countries.

Vanilla is the second-most expensive plant-derived flavouring in the world, after saffron, because growing the vanilla seed pods and hand-pollinating them is so labor-intensive. Despite the expense, vanilla is highly valued for its flavor, widely used in commercial and domestic baking, perfume manufacture and aromatherapy.[3]

> ***"I have no other means of survival. I just have to sell vanilla... [without it] we can no longer buy food, pay bills, medical bills, house rents, school fees." When told even the alternative crop, cocoa, might become synthesized, he said, "...then we prepare to die."***
>
> Jean Michel, vanilla farmer, Madagascar[7]

Vanilla as a Natural Product

Vanilla essence occurs in two forms. Real seedpod extract from the tropical orchid is an extremely complicated mixture of several hundred different compounds, including vanillin, acetaldehyde, acetic acid, furfural, hexanoic acid, 4-hydroxybenzaldehyde, eugenol, methyl cinnamate, and isobutyric acid. Of all these, the vanillin compound (4-hydroxy-3-methoxybenzaldehyde), a major contributor to the flavour and aroma of real vanilla, was first isolated from vanilla pods as early as 1858. Vanillin is now easily synthesized from various raw materials, but the majority of food-grade (>99% pure) vanillin is made from guaiacol in a solution of ethanol; it is usually synthesized from the wood-pulp residue of paper-making. Other sources, including the castoreum from the scent sac of beavers, may also be components in non-orchid-derived vanillin.[4] However, so many other compounds contribute to the complex vanilla flavour that the single component vanillin can only approximate. For this reason, real vanilla has never been fully replaced on the market and its "standard of identity" is closely regulated.

An estimated 200,000 people are involved in the annual production of cured vanilla beans worldwide. Industry analysts predict that the market for vanilla beans exports worldwide will reach an estimated $150 million US in 2013, with African producers accounting for approximately 64% of the total export market.[5]

Production of natural vanilla from vanilla beans uses a lot of workers: 1 kg of vanilla requires approximately 500 kg of vanilla pods and the hand-pollination of approximately 40,000 flowers. Madagascar and other island nations in the Southwest Indian Ocean (Comoros, Réunion) historically account for around three quarters of the world's vanilla bean production–and continue to dominate the market today. Vanilla bean production and processing is a vital cash crop in agroforestry systems where there are few alternative income sources. In Madagascar, an estimated 80,000 families cultivate vanilla orchids on approximately 30,000 hectares. In Comoros, about 5-10,000 families depend on vanilla bean production. Approximately 10,000 farm families cultivate vanilla orchids in Mexico, the geographic origin of vanilla. About 8,000 families in Central Africa (Uganda, Democratic Republic of Congo, Tanzania) also depend on vanilla bean production. In recent years Indonesia and China have become major vanilla bean producers; other producers include French Polynesia, Malawi, Tonga, Turkey and India.[6] In recent years, disease, storms, but especially synthetics (vanillin and soon, syn bio) have been taking more of the market share. The industry has been shaken to the extent that some worry that true vanilla could start disappearing from cultivation.[7]

So many poor livelihoods are affected worldwide that the swings in prices have alarmed many researchers. Programs from Fair Trade labeling to corporate and government alliances are trying to establish model farms where both inputs and prices can be stabilized for vanilla workers.[8]

Biodiversity and Cultural Considerations

By the 15th century, the Totonacs, who peopled the area now known as Veracruz on the east coast of Mexico, had passed on their use of the vanilla pod to the Aztecs, as both a valued tribute and a form of currency. The Totonacs called it the Fruit of the Gods, the Spanish valued it as an aphrodisiac. Because only a local bee had evolved to pollinate it, it wasn't until the 19th century that a 12 year-old slave boy far away on the island of Reunion learned how to hand-pollinate it. It then became a major crop in that area.[9]

The vanilla cropping system, especially in Madagascar, is regarded as a vital part of the maintenance and sustainability of agroforestry areas, which are mainly organic. The vanilla orchid vines rely on tropical forest shade and support, and require a great deal of work to cultivate, harvest and process. Because the vanilla orchid grows as a vine, climbing up an existing tree (also called a tutor), pole, or other support, it can be grown in a forest and so is closely linked to forest protection and conservation.[10]

In a 2014 interview with ETC Group, Madagascan vanilla farmer Tsara Samson from Sambava region explained that: "...The forest is protected by the people to help preserve their vanilla beans, because it needs to grow in the shadow the forest provides. If they can no longer grow vanilla because it has lost its value, the forest in most communities will be cleared." He went on to say that "Vanilla acts as an Environmental Protection for the forest, because [currently], they take care of the forest and the forest takes care of their vanilla, it's a win-win situation. They periodically plant trees to replenish the old ones, all because of the vanilla beans."[11]

Synthetic Biology Production

Evolva, a Switzerland-based synthetic biology company, has partnered with US industry giant International Flavors & Fragrances (IFF) to engineer metabolic pathways in microbes to produce key flavor compounds found in vanilla. In 2014 Evolva and IFF commercialized a biosynthesized vanillin flavor which is now sold as part of IFF's 'Always Vanilla' line.[12] Evolva has biosynthesized several molecules involved in the complex flavor profile of natural vanilla – primarily the substance vanillin. ETC Group understands that this new ingredient is already being incorporated into flavor mixes sold by IFF. Evolva maintains that simply because the product is fermented, this flavor (and any mixes that contain it), can be legally sold as a "natural flavour."

According to investment analysts, the company's key advantage is that its syn bio-based fermentation route allows Evolva to sell this so-called "natural" vanillin at a price that is lower than other natural vanilla flavours.[13] Evolva acknowledges that the flavor of the company's biosynthesized vanillin is not equivalent to the flavoring derived from the cured vanilla bean; but claims that the taste profile of vanillin produced by engineered yeast is more complex and closer to the natural vanilla flavor than artificial vanillin. Evolva has engaged in glossy, consumer-focused efforts, including a cartoon video, to overcome consumer resistance to syn bio vanillin. They feel they can market this new synthetic as being "more sustainable and higher quality."[14]

Implications and the Future

Despite high-profile corporate pledges to source raw materials ethically and sustainably, the world's largest brokers of flavor and fragrance ingredients (e.g., Givaudan, Firmenich and IFF) are partnering with synthetic biology companies for the biosynthesis of high-value flavor/fragrance molecules like vanilla. This move could dramatically reduce botanical imports and impoverish hundreds of thousands of small-scale farmers.

From the consumer's point of view, if government regulators continue to permit Evolva and IFF to market new, biosynthesized products such as the Always Vanilla product as “natural” consumers will not know if their flavor/fragrances are sourced from small farmers in the tropics, or from human-created microbes in giant fermentation tanks in industrial factories.

For the ingredients giants, the synthetic biology platform offers the potential to secure uninterrupted supplies of these high-value, flavor/fragrance/pharmaceutical plant compounds in industrial-scale fermentation tanks, instead of sourcing plant materials from equatorial farmers. Synthetic microbial cell factories are fully in the control of large corporations and less constrained by geography, extreme weather, crop failures and price volatility. They will remove the farm families whose livelihoods depend on cultivation of high-value botanical exports from the trade equation, and possibly make the forests less viable for preservation as well.

The commercial success of biosynthesized vanillin ultimately depends not just on competitive price or flavor, but on misleading the consumer with “natural” claims. Recent precedent suggests that biosynthesized vanillin produced via fermentation may indeed get away with carrying the “natural” label: Chemical giant Solvay (Belgium) already makes a vanillin ingredient via the fermentation of ferulic acid derived from rice bran. Government regulators have permitted Solvay’s vanillin to be labeled “Natural flavoring/Flavor/Vanilla flavor” (EU) or “Vanillin derived by a natural process” (US) and this appears to be the precedent Evolva and IFF are following, that misleads consumers.[15]

While Evolva insists that its biosynthesized vanillin is not designed to compete with farmer-grown vanilla beans, if the company succeeds in selling its vanillin flavor as “natural” and offers it at a fraction of the cost of botanically-derived vanilla, even cheaper than existing synthetic vanillins, then it may capture a significant portion of the already stressed natural vanilla bean flavor market, and harm tropical farmers.

Endnotes

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Vetiver

A Case Study on Use of Synthetic Biology Replacements

Farmers Affected: 27,000 families in Haiti (an estimated 60,000 people)

Market Value: 16 million USD per annum for Haiti. Globally approximately 50 million USD (250 tonnes/annum[1])

Uses: Scent and fixative in perfumes and fragrances

Syn Bio Companies: Evolva (formerly Allylix)

Hotspots: Haiti (100 tonnes), Java (100 tonnes)[2], India (20-25 tonnes),[3] and Réunion (20-30 tonnes)

Also Grown In: Indonesia, Philippines, Sri Lanka, China, Madagascar, Paraguay, Japan, Brazil, Africa (South Africa and West Africa)

Cultural Importance: Vetiver Oil, or the "fragrance of the soil" is cited in the Bhagavad Gita and has been used by Ayurvedic and Chinese medicinal practitioners for thousands of years.

Biodiversity Considerations: Erosion prevention and water filtration, landslide control, tidal flood control, fish production. Grass used for fallow lands, land demarcation, housing, fuel and fodder for the animals.

Quality Concerns: Natural vetiver oil has several constituents. Evolva/Allylix has synthesized only one of them (Beta-vetivone) which is also not the key vetiver compound (khusimone). So quality and richness is lower.

Patents: WO2008116056 A3, US8642815, US7622614 B2

Products: Used in 90% of Western perfumes.[4] Also household scented products

Method: Fermentation

Commercialization: Announced for 2012; Evolva has since said they will not commercialize for now.

Feedstock: Synthetically engineered yeast

Brand, Identifier: Epivone™

Overview

Vetiver (*Chrysopogon zizanioides*), or khus, is a perennial, densely tufted grass native to India. It is planted widely for its very efficient root system as a means of erosion prevention and water filtration. However, and most importantly, it is valued for the oil made from its roots that sells on the market at $200 US/kg. It may be used in 90% of all Western perfumes, and also in lotions, air fresheners, household products, ice creams, cosmetics and as a food preservative.

Status: Syn bio vetiver is delayed for now

R&D — Scale Up — Commercialization

In Haiti alone, vetiver oil production is the country's single most valuable agricultural export and supports an estimated 60,000 people. Java produces approximately the same amount of oil per year, and should be considered as supporting a comparable amount of farming families.

In 2012, Evolva announced Epivone™, its new, genetically engineered fragrance based on a key vetiver compound beta-vetivone which had never previously been synthesized. However, although the commercialization of this substance was slated for 2012, it has never been put on the market.

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

What is Vetiver?

Vetiver oil, a fragrance widely used in cosmetics and perfumes, is extracted from the aromatic roots of a perennial grass native to India (Chrysopogon zizanioides), commonly known as vetiver.

GQ Magazine has called it the "perfect natural raw material for a masculine scent." Known for its musty, woody odour, vetiver oil is also known for its fixative qualities, which means that it helps a fragrance to last longer after it is applied to the skin. Vetiver oil can be detected in the "base notes" of many perfumes or colognes. It is the basis of the Indian perfume "Majmua," and is reported to be contained in 90% of scented products,[6] while forming the major ingredient in some 36% of all Western perfumes (e.g. Caleche, Chanel No. 5, Dioressence, Parure, Opium) and 20% of mens' fragrances.[7] In addition to perfumes, vetiver oil is used in lotions, air fresheners, household products, ice creams, cosmetics and food preservation.

"The invention of cheap, synthetic alternatives to high-value agricultural exports such as vetiver could suddenly destabilize vulnerable economies by removing a source of income on which farmers rely."

World Economic Forum Global Risks Report 2015[5]

Vetiver as a Natural Product

Vetiver is closely associated with the country of Haiti. Haiti's vetiver crop is processed by 10 distillers, but it provides jobs for some 27,000 farming families in the southwest. For these farmers, the vetiver plant also has important conservation benefits, preventing soil erosion and helping maintain water quality.

Annual world trade of vetiver is an estimated 250 tonnes. Major commercial producers include Haiti, Java, India, Réunion, China, Japan, Indonesia and Brazil. For at least two island nations, Haiti and Réunion, the essential oil obtained from the roots of vetiver is a major source of foreign exchange earnings. Haiti's share of worldwide vetiver exports grew from 40% in 2001 to over 60% in 2007. In the wake of the worldwide financial crisis however, Haiti has seen a sharp reduction in vetiver exports. Haiti produces about 50 to 100 tonnes of vetiver annually, up to half of the world's supply.

An estimated 60,000 people in Haiti's Les Cayes region depend on vetiver as their primary income source; the crop is grown on 10,000 hectares. The region also supports up to 10 distilleries that process and extract vetiver oil for export employing and benefiting yet more people. Before 2009, Haiti's vetiver crop was valued at approximately $15-$18 million per annum. In recent years, Haiti's export earnings from vetiver have declined to around $10 million per annum.

Indonesia had been the second largest vetiver oil-exporting country in the world after Haiti; however, following Haiti's 2010 earthquake, Indonesia appears to be the leading exporter of this valuable oil.[8]

Planting vetiver grass in Kenya 2010

Biodiversity and Cultural Considerations

Vetiver grass thrives in harsh environments. It can be cultivated on steep hillsides, and used for landslide control. In coastal areas vetiver is grown for tidal flood control; in marshes, it is grown to aid fish production.

The vetiver plant provides vital natural protection against soil erosion and helps maintain water quality. Vetiver has a strong, fibrous root system which rapidly penetrates deep into the soil and develops into a tightly-knit net. The roots absorb soil nutrients and chemical substances, protecting water sources from chemical fertilizers and pesticides. Farmers also use vetiver to regulate soil moisture, recharge groundwater, recycle soil nutrients and control pests.[9] Vetiver is a wonder grass for low income farmers, who can plant it in their fallow lands, use it for land demarcation and as housing, fuel and fodder for their animals.[10]

Vetiver Oil, or the "fragrance of the soil" as cited in the Bhagavad Gita, has been used by Ayurvedic and Chinese medicine practitioners for thousands of years and was used for massaging brides to sanctify them before marriage in India.

Synthetic Biology Production

A California-based synthetic biology company, Allylix, Inc. (now purchased by Evolva), has engineered a metabolic pathway in microbes to produce beta-vetivone through fermentation; beta-vetivone is one of three key fragrance compounds found in vetiver oil. In March 2012, Allylix, Inc. announced that it would begin commercial sale of its new vetiver fragrance, called "Epivone™," in the third quarter of 2012. The company estimated that sales of similar terpene molecules used in fragrance applications would amount to between $20 and $200 million dollars per year.[11]

However, since the 2014 acquisition of Allylix, Evolva has not publicly disclosed plans for further research, development or commercialization related to beta-vetivone i.e. Epivone™. The company's website does not mention Epivone™ or the potential market for a vetiver-related fragrance. ETC Group contacted Evolva's CEO, Neil Goldsmith about the company's plans to commercialize its Epivone™ product. According to Mr. Goldsmith: "No, we are not developing Epivone. Allylix decided not to commercialize it, and we have no plans to revisit that decision. Is that a 'no, never?' No it is not. But I think it is highly unlikely."[12]

Freshly harvested vetiver plants   Photo (cc) Josuah

Implications and the Future

Evolva told ETC Group that the decision to halt commercialization had already been made by Allylix before it was acquired by Evolva. We suspect that the high profile support for Haitian vetiver by philanthropic organizations, plus concerns already raised by ETC Group and our allies about Epivone impacting vetiver farmers, was seen as a public relations liability. It would also detract from Evolva's most strategically important "natural" products (especially engineered stevia, in partnership with Cargill).

Chemists have so far been unable to achieve chemical synthesis of vetiver essential oil – although key aroma compounds (such as khusimone) have been synthesized.[13]

There is no assurance that vetiver-related fragrance compounds will not be the target of Evolva or other synthetic biology researchers/companies in the future and at this point Evolva appears to be retaining the patents on Epivone. If Evolva or another company move ahead with commercializng vetiver compounds, this can seriously impact the market for botanically-derived vetiver, as well as the livelihoods of around tens of thousands of farming families in Haiti. This was highlighted in a recent "global risks" report by the World Economic Forum, which pointed out that, "The invention of cheap, synthetic alternatives to high-value agricultural exports such as vetiver could suddenly destabilize vulnerable economies by removing a source of income on which farmers rely." [14]

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Synthetic Biology, Biodiversity and Farmers

Case studies exploring the impact of synthetic biology on natural products, livelihoods and sustainable use of biodiversity

A fundamental shift is underway in how food, flavor, cosmetic and fragrance ingredients are being produced for global markets.

The new game in town is ***biosynthesis:*** the artificial production of key compounds by synthetically engineered organisms.

In this report ETC Group presents a series of case studies outlining how current livelihoods from traditional agricultural production may be adversely affected as these synthetic biology-based substitutes enter the market.

Several of these synthetic substitutes are already in commercial use, displacing farmers and impacting biodiversity in their wake.

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