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What's That Smell? Exotic Scents Made From Re-engineered Yeast

By ANDREW POLLACK

EMERYVILLE, Calif. — Vanilla, saffron, patchouli. For centuries, spices and flavorings like these have come from exotic plants growing in remote places like the jungles of Mexico or the terraced hillsides of Madagascar. Some were highly prized along ancient trading routes like the Silk Road.

Now a powerful form of genetic engineering could revolutionize the production of some of the most sought-after flavors and fragrances. Rather than being extracted from plants, they are being made by genetically modified yeast or other micro-organisms cultured in huge industrial vats.

"It's just like brewing beer, but rather than spit out alcohol, the yeast spits out these products," said Jay D. Keasling, a co-founder of Amyris, a company based here that is a pioneer in the field. However, while yeast makes alcohol naturally, it would not produce the spices without the extensive genetic rejiggering, which is called synthetic biology.

The advent of synthetic biology raises thorny economic and regulatory issues, such as whether such yeast-made ingredients can be called natural and whether developing countries dependent on these crops will be hurt.

Supporters say the technique could benefit food and cosmetic companies, and ultimately consumers, by reducing wild swings in price, availability and quality that come from dependence on agriculture. It may even relieve pressure on some overharvested wild plants like sandalwood, a tree that provides a fragrance.

The products, which taste or smell nearly the same as the real thing, are coming quickly and even moving beyond flavors and fragrances to include other commodities, like rubber and drugs.

In April, the pharmaceutical company Sanofi began commercial production of an essential malaria drug using baker's yeast genetically modified by Amyris. The drug's ingredient is usually extracted from a shrub that grows wild or is cultivated in China, Vietnam and various

African countries. Amyris is also making a moisturizer for cosmetics that is typically extracted from either olives or shark livers.

Evolva, a Swiss company, is about to start marketing yeast-made vanillin, the main component of vanilla. It is also working on saffron, now obtained mainly from crocuses grown in Iran.

Two other companies, Isobionics and Allylix, are separately producing valencene, a flavoring usually extracted from oranges, and nootkatone, a grapefruit flavor that also has potential as an insect repellent.

"It's really environmentally friendly. The whole process is sustainable," said Toine Janssen, chief executive of Isobionics, based in the Netherlands.

But critics say the technology threatens the livelihoods and exports of developing countries. "They are going after pockets of tropical farmers around the world," said Jim Thomas, a researcher at the ETC Group, a Canadian technology watchdog.

Rick Brownell, an executive at the Virginia Dare Extract Company, a leading supplier of natural vanilla based in Brooklyn, said 80,000 farmers in Madagascar, one of the world's poorest countries, grow vanilla beans.

"I really count on that to make a living," said Bersonina, 63, a farmer in Madagascar. Bersonina, who uses only one name, said in a telephone interview arranged by the company that the $200 he made last year producing about 50 kilograms, or 110 pounds, of vanilla barely supported his family of four. He said he was not familiar with the yeast-made vanilla substitute but imagined that an industrial process "could make thousands and thousands of tons," posing a threat to farmers like himself.

Chemically synthesized substitutes for vanillin and other extracts already exist and fermentation has long been used to make some vitamins and citric acid. But proponents of synthetic biology say that the more extensively modified yeast can make things that cannot be synthesized chemically and could not previously be made by fermentation. They also say the resulting products might be more natural than chemical substitutes.

"The need for natural is the key driver," said Ahmet Baydar, director of research and development at International Flavors and Fragrances, the big flavorings company that will market Evolva's vanillin.

Evolva's vanillin cannot be called natural vanilla, because the vanilla bean product contains scores of components besides vanillin. But it conceivably could be called a natural ingredient

since it is made in a living organism, said John B. Hallagan, general counsel of the Flavor and Extract Manufacturers Association.

International Flavors and Fragrances is hoping that the vanillin will be attractive to food companies that want to label their products all-natural but do not want to pay the higher price for natural vanilla.

But the environmental group Friends of the Earth has started a campaign to pressure ice cream makers into rejecting the vanillin. "There's nothing 'natural' about genetically engineered yeast that excretes vanilla flavoring," it said in an August e-mail to members.

Another issue is whether foods containing such ingredients will need to be labeled made from genetically modified organisms in countries that require such labeling. The flavor companies say they do not think so because the yeast is considered a processing aid, not a source of the food.

The United States does not require labeling, though there are legislative efforts in various states to do so.

Yeast already makes some compounds in the same broad family as those Amyris hopes to produce. The company substitutes some genes to change the end product. Amyris also engineers the yeast so it devotes almost all its resources to produce the desired product.

"We are trying to maximize the flow in that pipe and pinch off all the side pipes without killing the organism," said Joel Cherry, the company's president for research and development.

By shuffling DNA, partly by design and partly at random, robotic systems at Amyris produce and test tens of thousands of yeast strains a month. The best-performing ones eventually end up in commercial production in 200,000-liter fermenters in Brazil, close to the sugar cane needed to feed the yeast.

The small start-ups are attracting bigger partners.

BASF, the German chemical company, is an investor in Allylix, the San Diego company that is using yeast to make orange and grapefruit extracts. It has also developed a product similar to a major component of vetiver oil, widely used in perfumes because of its woody aroma. Vetiver oil is extracted from a grass grown by thousands of small farmers in Haiti and some other countries.

Amyris is working on a rubber product with Michelin and is believed to be working on patchouli with Firmenich, a Swiss flavor and fragrance company. Evolva is working with Cargill on stevia, a sweetener extracted from plants grown in China and elsewhere.

The companies say their products can be cheaper than those from plants, though some experts say that has yet to be proved.

"You would have to have a very high yield to compete with plants that are so good at doing this," said Peter Facchini, a plant biologist at the University of Calgary. He is also a leader of Canada's PhytoMetaSyn Project, which is looking at engineering yeast to synthesize products from a wide variety of plants, including chamomile and cannabis.

Dr. Facchini wants to produce morphine from yeast, replacing the need for opium poppies. But he said yeast would not be cost-competitive with poppies for illegal drugs. "The Taliban is disinterested in synthetic biology," he said, a reference to the opium trade in Afghanistan.

Executives of the synthetic biology companies say their products, by relieving shortages and perhaps lowering prices, will expand markets, not displace farmers. But the mere prospect of new competition might prompt farmers to stop planting a crop, producing a shortage before enough yeast-made product is available.

That is a concern now with artemisinin, a malaria drug derived from Artemesia annua, or sweet wormwood. Amyris's project to make that drug using yeast, which was financed largely by a $42.6 million grant from the Bill and Melinda Gates Foundation, was initially described as a way to stabilize supply of a vital medicine, since the natural product has been subject to great swings in price and availability.

But at a conference in April, Dr. Keasling, the co-founder of Amyris, said there were "moves afoot" to supply the entire world demand from the synthetic biology product.

"That sent shock waves through the industry," said Malcolm Cutler, a principal at A2S2, a project aimed at ensuring an adequate supply of artemisinin. He said some Artemisia growers were contemplating not planting.

"If we get this wrong, people are going to die," he said.

Dr. Keasling, who is also a professor of chemical engineering at the University of California, Berkeley, said that some small Artemisia farmers were being put out of business by larger plantations, not by synthetic biology. In any case, he said, the priority was to reduce the cost and increase the availability of the malaria drug. "It's about saving the lives of children," he said.