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GABA-enriched tomato is first CRISPR-edited food to enter market

Sanatech Seed's Sicilian Rouge CRISPR-edited 'health-promoting' tomatoes reach consumers and may open the market to more genome-edited fruit, vegetables and even fish.

Emily Waltz

A CRISPR-edited tomato containing higher GABA than its unedited counterparts takes off in Japan. Credit: Aflo Co., Ltd. / Alamy Stock Photo

Genome-edited food made with CRISPR–Cas9 technology is being sold on the open market for the first time. Since September, the Sicilian Rouge tomatoes, which are genetically edited to contain high amounts of γ-aminobutyric acid (GABA), have been sold direct to consumers in Japan by Tokyo-based Sanatech Seed. The company claims oral intake of GABA can help support lower blood pressure and promote relaxation.

In Japan, dietary supplements and foods enriched for GABA are popular among the public, says Hiroshi Ezura, chief technology officer at Sanatech and a plant molecular biologist at the University of Tsukuba. “GABA is a famous health-promoting compound in Japan. It’s like vitamin C,” he says. More than 400 GABA-enriched food and beverage products, such as chocolates, are already on the Japanese market, he says. “That’s why we chose this as our first target for our genome editing technology,” he says.

Sanatech, a startup from the University of Tsukuba, first tested the appetite of consumers in Japan for the genome-edited fruit in May 2021 when it sent free seedling CRISPR-edited tomato plants to about 4,200 home gardeners who had requested them. Encouraged by the positive demand, the company started direct internet sales of fresh tomatoes in September and a month later took orders for seedlings for next growing season. Japan’s regulators approved the tomato in December 2020.

Since its inception a decade ago, CRISPR–Cas9 genome editing has become a tool of choice for plant bioengineers. Researchers have successfully used it to develop non-browning mushrooms, drought-tolerant soybeans and a host of other creative traits in plants. Many have received a green light from US regulators. But

before Sanatech's tomato, no CRISPR-edited food crops were known to have been commercialized.

Consumers may find food ingredients made with some of the older DNA editing techniques, such as transcription activator-like effector nucleases (TALENs). Indeed, Calyxt in 2019 commercialized a TALEN-edited soybean oil that is free of *trans* fats. Genome editing tools have also been used to transform a host of ornamental plants. So it was only a matter of time before a CRISPR-edited crop reached palates.

More interesting, however, is that the developer chose this high GABA trait as a first target. GABA is an amino acid and a neurotransmitter that blocks impulses between nerve cells in the brain. The molecule is found natively in the human body and is also ubiquitously present in plants, animals and microorganisms, as well as in food. It can be synthesized by fermenting food and has been developed as a nutritional supplement in some regions.

Sanatech's researchers increased the amount of GABA in tomato by manipulating a metabolic pathway called the GABA shunt. There, they disabled a gene that encodes calmodulin-binding domain (CaMBD). Removal of CaMBD enables increased activity of the enzyme glutamic acid decarboxylase, which catalyzes the decarboxylation of glutamate to GABA, thus raising levels of the molecule.

Sanatech has been careful not to claim that its tomatoes therapeutically lower blood pressure and promote relaxation. Instead, the company implies it, by advertising that consuming GABA, generally, can achieve these effects and that its tomatoes contain high levels of GABA. This has raised some eyebrows in the research community, given the paucity of evidence supporting GABA as a health supplement.

To support the blood-pressure assertion, Sanatech cites two human studies: a 2003 paper on the effect of consuming fermented milk containing GABA and a 2009 paper of the effects of GABA, vinegar and dried bonito. Both studies were conducted in people with mild hypertension and showed blood-pressure-lowering effects.

But the papers lack good control groups, and the effects in the experimental groups could be explained by factors other than GABA, says Maarten Jongsma, a molecular cell biologist at Wageningen University & Research in the Netherlands, who studies the effects of plant compounds on human nutrition. “There’s no consensus” on the health benefits of consuming GABA, nor evidence that it can cross the blood–brain barrier and reach the central nervous system, adds Renger Witkamp, a nutrition scientist also at Wageningen.

To support the claim that GABA promotes relaxation, Sanatech points to six studies in humans that examined the effect of orally consumed GABA on stress, mood, fatigue or sleep. But a systematic review published in 2020 that examined all six of these papers plus eight more on the topic came to a different conclusion. The authors, who hailed from Japan, Australia and the United Kingdom, summarized: “There is limited evidence for stress and very limited evidence for sleep benefits of oral GABA intake.”

Sanatech’s tomatoes, called the Sicilian Rouge High GABA, contain about four to five times more GABA than their conventional counterpart, Ezura says. Whether that will lower blood pressure any more than eating regular tomatoes is unclear. Sanatech has not performed this kind of intervention study, although it plans to do so, Ezura says. The company is working to complete an additional notification with the Japanese government on the health benefit claim.

Sanatech's marketing strategy has been to target consumers directly and generate positive buzz among home gardeners. The company created an online platform for gardeners to swap tips. It also held a contest to see which home gardener could grow tomatoes with the highest amount of GABA. (The winning tomato had 20 times more GABA than conventional tomatoes.)

That's a smart marketing strategy for genome-edited fruit and vegetables, especially those with boutique traits, says Cathie Martin, a plant scientist at the John Innes Centre in Norwich, UK. "You find a group of people who feel as though they have some ownership of the product," she says. You then help build up a community of people who want to grow and eat the vegetable, and this launches the product on a positive track, she says.

Martin is the creator of the 'purple tomato', a variety that is genetically modified to contain higher levels of the anti-inflammatory compound anthocyanin, which she debuted in 2008 in these pages. Over the past 14 years, without the resources of a large company, she and an "un-financed, dedicated band of enthusiasts" have been trying to push the product to market on their own, she says.

Her challenge of commercializing a bioengineered crop is one that most small plant biotech companies have also faced, particularly those developing boutique varieties. "The regulatory cost is so high that there are very few traits that you could actually even consider engineering in a crop like tomato," says James Giovannoni, a plant molecular biologist at the Agricultural Research Service at the US Department of Agriculture (USDA). That's why, since the mid-1990s, most commercial efforts in the genetic engineering of plants have focused on high-dollar crops, such as soybean, corn (maize), wheat, canola and cotton, with traits that make farmer's jobs easier and their harvests more profitable.

Meanwhile, nutritionally enhanced crops have been stillborn. The few examples on the market include soybeans and canola with modified oil and fatty acid content, and nutritionally improved corn for animal feed. Scores more, such as the high β-carotene super-banana, have been developed but sit in limbo on laboratory shelves. The storied 'golden rice', which is enhanced with provitamin A and has been in limbo for 20 years, just a few months ago received approval in the Philippines for commercial cultivation.

So Sanatech's high-GABA tomato, as a nutritionally enhanced crop, stands out. The fact that it was engineered using CRISPR seems to help with consumer acceptance, especially as such crops aren't being called "GMOs," or "genetically modified organisms." Instead, they're dubbed "genome-edited." This change in nomenclature alone seems to have quelled a lot of the backlash historically launched against bioengineered plants.

Some regulators are making a distinction between the old and new technologies too. The USDA has repeatedly ruled that genome-edited crops fall outside of its purview. Plant biotechnologists who submit such inquiries through the agency's "Am I Regulated?" process typically get a response within a few months and receive a green light to grow their genome-edited plants without further oversight.

This has reduced the US regulatory burden for genome-edited plants to next to nothing. Brazil, Argentina and Australia have taken a similar approach. China has established a regulatory process for genome-edited agricultural organisms, although none has yet been approved, says Hongliang Zhu, a professor at China Agricultural University in Beijing, speaking on behalf of himself and not his employer or government. Europe has essentially banned genome-edited foods, lumping them in with first-generation GMOs, although there have been calls to

rethink the policy.

Many other countries still lack any policy on the technology, slowing commercial efforts. Toolgen in Seoul, South Korea, has used CRISPR to generate color-modified petunias, high-oleic acid soybeans and browning-inhibited potatoes, "but they are not on sale yet because the domestic regulatory policy for CRISPR genome-edited crops has not been established," says Yein Joen, a researcher at the company.

Japan's regulatory policy on genome-edited plants formed in tandem with its review of Sanatech's tomato — a process that took about a year. Ezura "deserves great credit for single-handedly pushing the Japanese government to institute a policy where gene-edited crops can be brought to market," says Harry Klee, a plant molecular biologist and tomato researcher at the University of Florida. "This is a big deal in Japan and he did a great job."

Ezura's efforts have opened the door for genome-edited food in Japan. In November, researchers at Nagoya University described in Scientific Reports a sweeter tomato developed by modifying a cell wall invertase inhibitor using CRISPR–Cas9. The variety has not been approved by regulators.

And CRISPR–Cas9 edited food in Japan has leapt from the garden to the sea. In October, the island nation approved two CRISPR-edited fish: a gene-edited tiger puffer that exhibits depressed appetite suppression and a red sea bream with increased muscle growth. Both fish grow larger than their counterparts in the wild and were developed by the Kyoto-based Regional Fish Institute.

For Martin, it wasn't possible to confer the anthocyanin trait in her purple tomatoes using genome editing. Instead, she transformed them using *Agrobacterium tumefaciens*, an older method of genetic modification that

triggers considerably more regulatory oversight and resources, along with the moniker “GMO.” But the door to market may soon open for her too. Martin says she expects a regulatory decision from the USDA by the end of February for purple tomatoes. Like Sanatech, Martin plans to initially market them directly to the public. She has not conducted human intervention studies comparing the health effects of high-anthocyanin and conventional tomatoes, and does not plan to make health benefit claims.

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