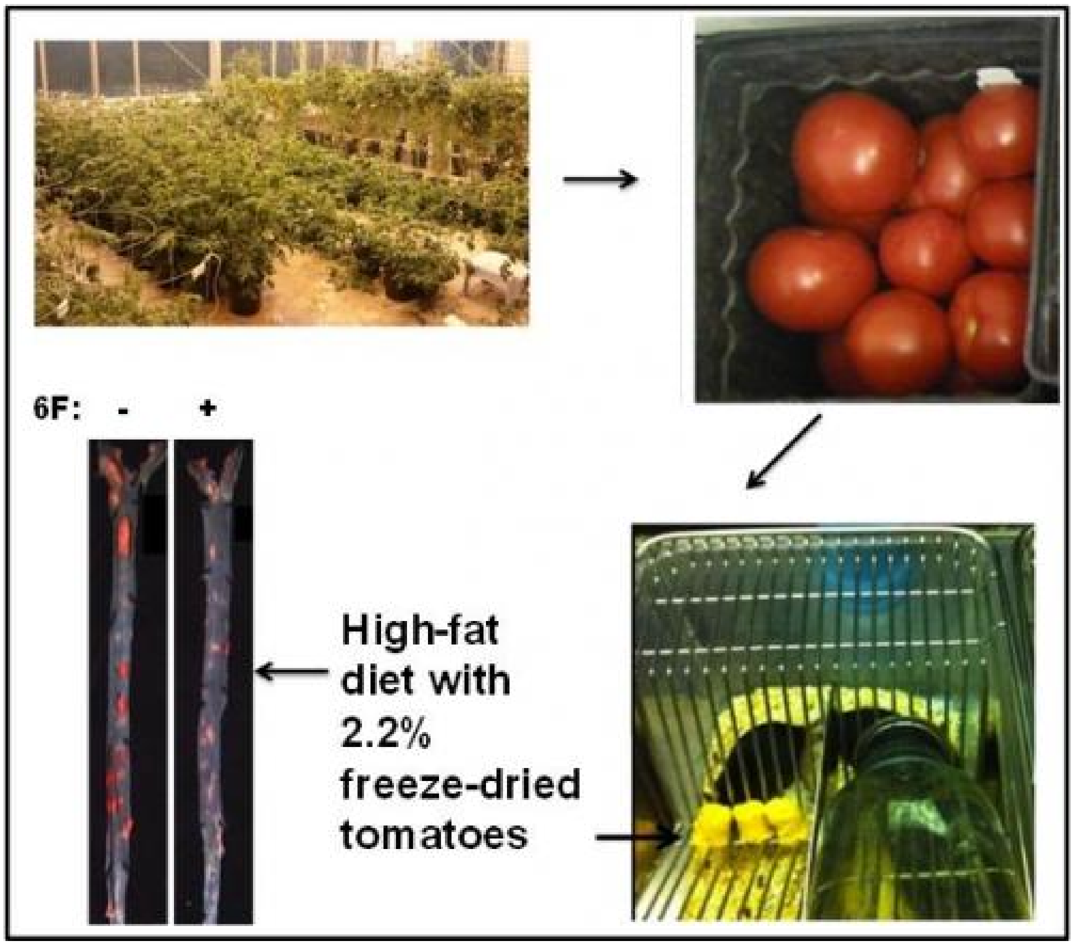
Researchers create tomatoes that mimic actions of good cholesterol

March 19 2013



Images demonstrate growing and harvesting genetically-engineered tomatoes that produce 6F, a small peptide that mimics the action of the chief protein in HDL. The tomatoes were freeze-dried and made up 2.2 percent of a high-fat diet fed to mice in the study. Note less cholesterol build-up (in red) in the artery of the mouse fed tomatoes with 6F versus the mouse that ate the high-fat diet containing 2.2 percent freeze-dried control tomatoes that did not contain 6F. Credit: UCLA

UCLA researchers have genetically engineered tomatoes to produce a peptide that mimics the actions of good cholesterol when consumed.

Published in the April issue of the *Journal of Lipid Research* and featured on the cover, their early study found that mice that were fed these tomatoes in freeze-dried, ground form had less inflammation and plaque build-up in their arteries.

"This is one of the first examples of a peptide that acts like the main protein in good cholesterol and can be delivered by simply eating the plant," said senior author Dr. Alan M. Fogelman, executive chair of the department of medicine and director of the atherosclerosis research unit at the David Geffen School of Medicine at UCLA. "There was no need to isolate or purify the peptide—it was fully active after the plant was eaten."

After the tomatoes were eaten, the peptide surprisingly was found to be active in the small intestine but not in the blood, suggesting that targeting the small intestine may be a new strategy to prevent diet-induced atherosclerosis, the plaque-based disease of the arteries that can lead to heart attacks and strokes.

Specifically for the study, the team genetically engineered tomatoes to produce 6F, a small peptide that mimics the action of apoA-1, the chief protein in high-density lipoprotein (HDL or "good" cholesterol). Scientists fed the tomatoes to mice that lacked the ability to remove low-density lipoprotein (LDL or "bad" cholesterol) from their blood and readily developed inflammation and atherosclerosis when consuming a high-fat diet.

The researchers found that mice that ate the peptide-enhanced tomatoes, which accounted for 2.2 percent of their Western-style, high-fat diet, had significantly lower levels of inflammation; higher paraoxonase activity, an antioxidant enzyme associated with good cholesterol; higher levels of good cholesterol; decreased lysophosphatidic acid, a tumor-promoter that accelerates plaque build-up in the arteries in animal models; and less atherosclerotic plaque.

Several hours after the mice finished eating, the intact peptide was found in the small intestine, but no intact peptide was found in the blood. According to researchers, this strongly suggests that the peptide acted in the small intestine and was then degraded to natural amino acids before being absorbed into the blood, as is the case with the other peptides and proteins in the tomato.

"It seems likely that the mechanism of action of the peptide-enhanced tomatoes involves altering lipid metabolism in the intestine, which positively impacts cholesterol," said the study's corresponding author, Srinavasa T. Reddy, a UCLA professor of medicine and of molecular and medical pharmacology.

Previous studies performed by Fogelman's lab and other researchers around the world in animal models of disease have suggested that a large number of conditions with an inflammatory component—not just atherosclerosis—might benefit from treatment with an apoA-1 mimetic peptide, including Alzheimer's disease, ovarian and colon cancer, diabetes, asthma, and other disorders.

The immune system normally triggers an inflammatory response to an acute event such as injury or infection, which is part of the natural course of healing. But with many chronic diseases, inflammation becomes an abnormal, ongoing process with long-lasting deleterious effects in the body.

If the work in animal models applies to humans, said Fogelman, who is also the Castera Professor of Medicine at UCLA, consuming forms of genetically modified foods that contain apoA-1–related peptides could potentially help improve these conditions.

The peptide would be considered a drug if given by injection or in a purified pill form, but when it is a part of the fruit of a plant, it may be no different from a safety standpoint than the food in which it is contained—and it may be better tolerated than a drug, Fogelman said. He noted that one possibility could be the development of the peptide into a nutritional supplement.

The current study and findings resulted from years of detective work in searching for an apoA-1 peptide that could be practically produced. Peptides prior to the current 6F version have required additions that can only be made by chemical synthesis. The 6F peptide does not require these additions and can therefore be produced by genetically engineering plants.

The team chose a fruit—the tomato—that could be eaten without requiring cooking that might break down the peptide. The researchers were able to successfully genetically express the peptide in tomato plants, and the ripened fruit was then freeze-dried and ground into powder for use in the study.

"This is one of the first examples in translational research using an edible plant as a delivery vehicle for a new approach to cholesterol," said Judith Gasson, a professor of medicine and biological chemistry, director of UCLA's Jonsson Comprehensive Cancer Center and senior associate dean for research at the Geffen School of Medicine. "We will be closely watching this novel research to see if these early studies lead to human trials."

In addition, Gasson noted that this early finding and future studies may yield important and fundamental knowledge about the role of the intestine in diet-induced inflammation and atherosclerosis.

Provided by University of California, Los Angeles