Thunder god vine used in traditional Chinese medicine is a potential obesity treatment

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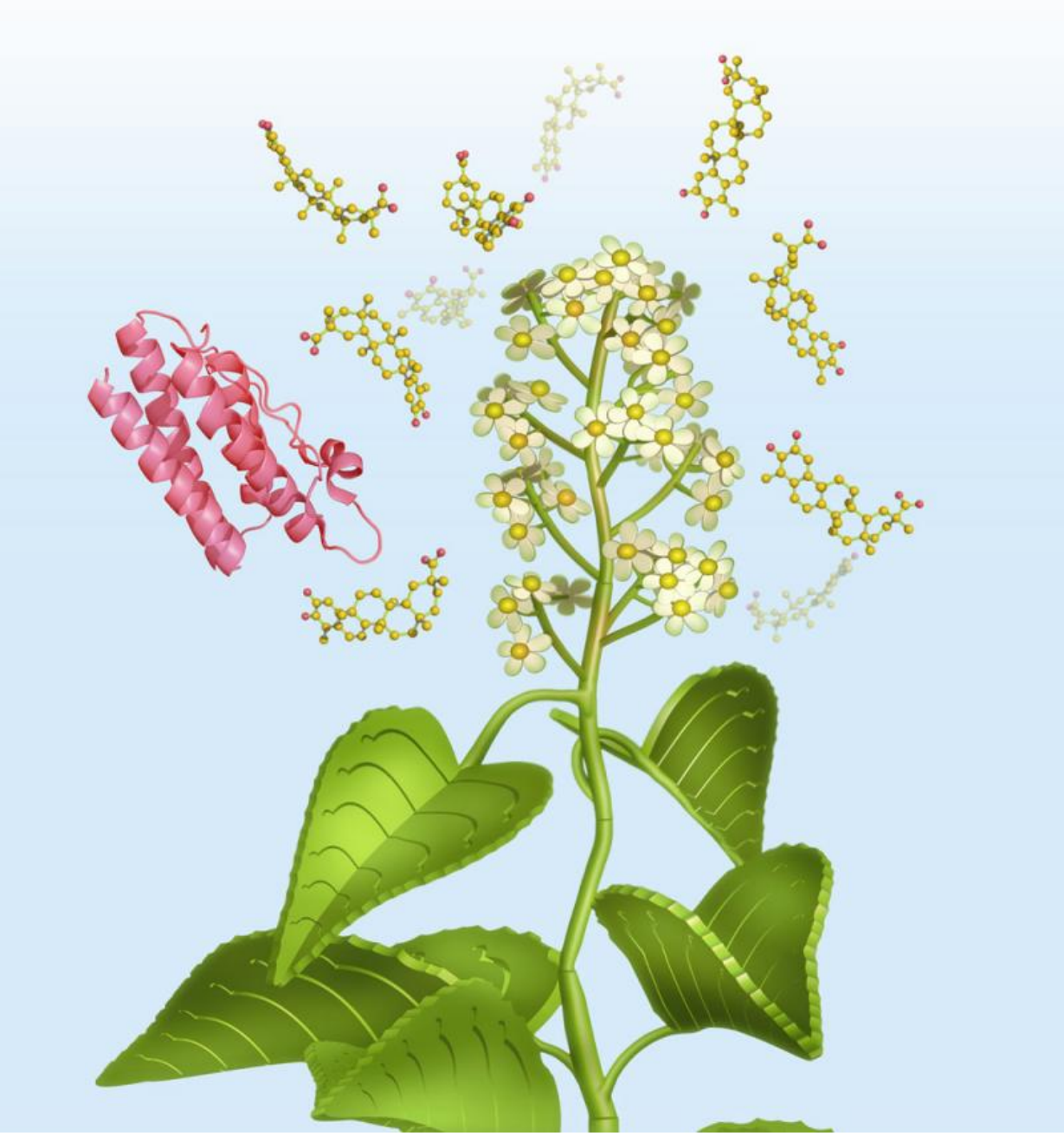


An artist's depiction of the thunder god vine and leptin molecule. Credit: Eric Smith

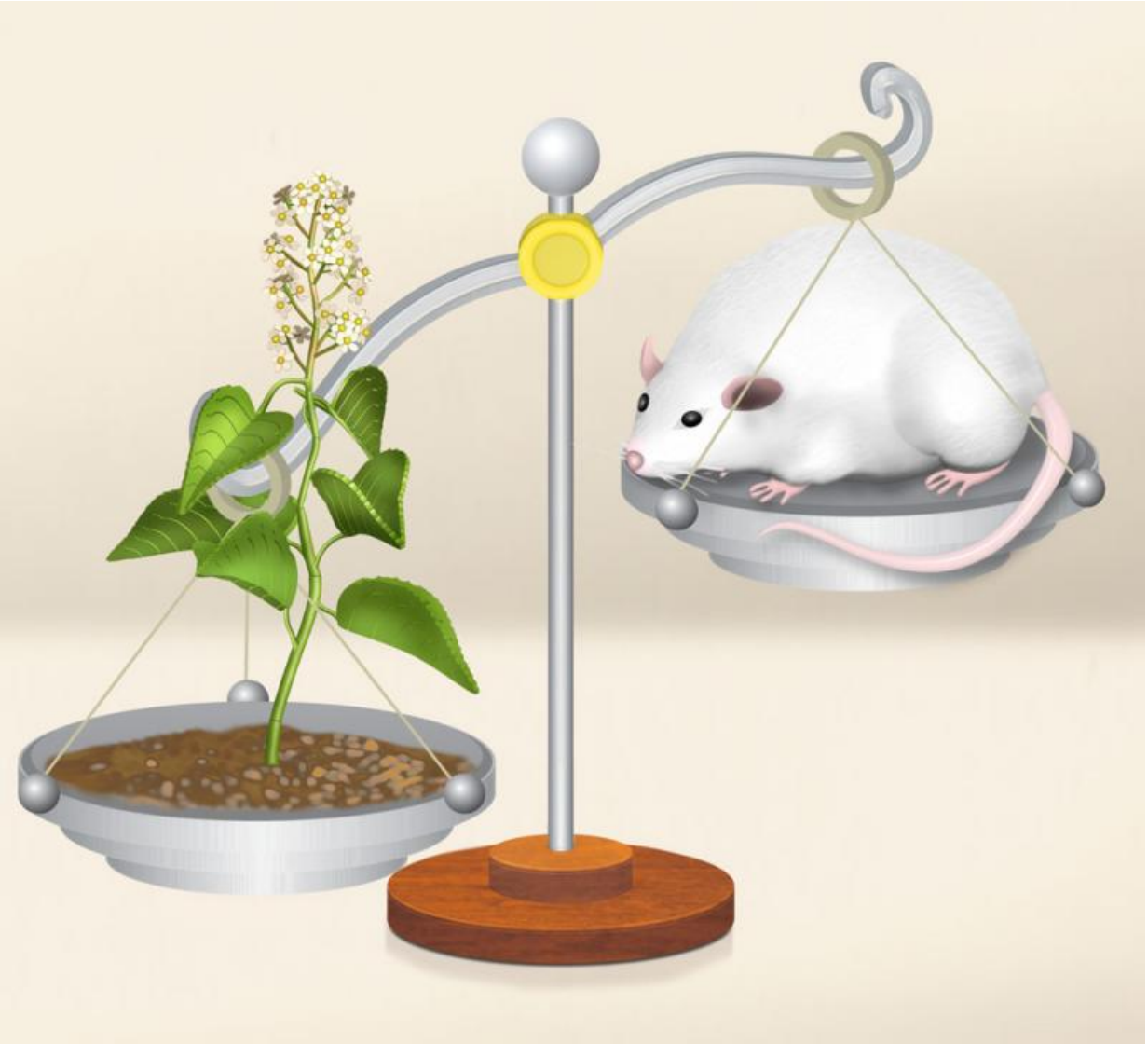
An extract from the thunder god vine, which has a long history of use in traditional Chinese medicine, reduces food intake and causes up to a 45% decrease in body weight in obese mice. The weight-loss compound, called Celastrol, produces its potent effects by enhancing the action of an appetite-suppressing hormone called leptin. The findings, published May 21 in *Cell*, are an early indicator that Celastrol could be developed into a drug for the treatment of obesity.

"During the last two decades, there has been an enormous amount of effort to treat obesity by breaking down leptin resistance, but these efforts have failed," says senior study author Umut Ozcan, an endocrinologist atBoston Children's Hospital and Harvard Medical School. "The message from this study is that there is still hope for making leptin work, and there is still hope for treating obesity. If Celastrol works in humans as it does in mice, it could be a powerful way to treat obesity and improve the health of many patients suffering from obesity and associated complications, such as heart disease, fatty liver, and type 2 diabetes."

Leptin is a fat-cell-derived hormone that signals to the brain when the body has enough fuel and energy. Humans and mice that lack leptin signaling eat voraciously and become morbidly obese, suggesting that leptin-enhancing drugs may be effective for treating obesity. But leptin does not reduce hunger or food intake in obese individuals despite high levels of the hormone in the bloodstream, leading many researchers to speculate that leptin insensitivity is the root cause of obesity. Despite

longstanding research efforts, drugs that can effectively alleviate leptin resistance have not yet been found. However, one potential clue to this problem came several years ago when Ozcan and his team discovered that leptin resistance is associated with a stress response in a cell structure called the endoplasmic reticulum (ER).

In the new study, Ozcan and his team screened an existing database containing whole-genome gene expression profiles from human cells that were treated with more than one thousand small molecules. They found that Celastrol was the most effective at producing an expression profile that could be associated with improved ER function and leptin sensitivity in human cells. Within only one week of Celastrol treatment, obese mice reduced their food intake by about 80% compared to untreated obese mice. By the end of the third week, treated mice lost 45% of their initial body weight almost entirely by burning fat stores.



An artist's depiction of the thunder god vine vs. obesity in mice. Credit: Eric Smith

This dramatic weight loss is greater than that produced by bariatric surgery—an operation on the stomach and/or intestines that helps patients with extreme obesity to lose weight. Moreover, Celastrol decreased cholesterol levels and improved liver function and glucose metabolism, which collectively may translate into a lower risk of heart

disease, fatty liver, and type 2 diabetes.

Even though Celastrol did not produce toxic effects in mice, Ozcan strongly urges caution for now because in-depth toxicology studies and controlled clinical trials are needed to demonstrate the compound's safety in humans. "Celastrol is found in the roots of the thunder god vine in small amounts, but the plant's roots and flowers have many other compounds," he says. "As a result, it could be dangerous for humans to consume thunder god vine extracts to lose weight."

In future studies, Ozcan and his team will investigate the molecular mechanisms by which Celastrol improves leptin sensitivity and produces weight loss. "We have been heavily focusing on this line of research in my laboratory and hope that this approach will help us to understand the mechanisms in nature that are leading to the development of obesity," Ozcan says. "In the end, my main goal is to see this research leading to a novel and powerful treatment for obesity in humans."

More information: *Cell*, Liu et al. "Treatment of Obesity with Celastrol" dx.doi.org/10.1016/j.cell.2015.05.011

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