

# Research team treats pulmonary hypertension through the leaves of plants

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The Penn-UF team developed a pulmonary hypertension treatment delivered through capsules containing freeze-dried plant leaves.

Researchers at the University of Pennsylvania and the University of Florida have identified a drug that can be used to treat pulmonary hypertension, a disease for which few therapy options exist. The novelty is the way the medicine is delivered; it is grown in the leaves of plants

from Penn's high-tech greenhouse, according to the study published online in the September issue of the journal *Hypertension*.

Henry Daniell was a senior author on the study. He is professor of biochemistry and pathology and director of translational research at Penn's School of Dental Medicine. Fellow Penn Dental Medicine authors included postdoctoral associate Kwang Chul-Kwon and research assistants Shina Lin and Guiying Jin. The Penn team collaborated with researchers from the University of Florida, including Vinayak Shenoy, an assistant research scientist in the College of Pharmacy Department of Pharmacodynamics; co-senior author Mohan Raizada, a distinguished professor of physiology and functional genomics in the Evelyn F. and William L. McKnight Brain Institute; and Michael Katovich, a professor in the College of Pharmacy.

In patients with [pulmonary hypertension](#), the arteries of the lungs become constricted, which increases the workload on right side of the heart to pump blood through the lungs. Over time, the right chamber of the heart, which usually is small, becomes enlarged and dysfunctional.

Currently, the most successful drugs for the disease cost tens of thousands of dollars.

"Pulmonary hypertension is relatively a rare disease. It's been neglected by the industry, and so there aren't many drugs out there," said Shenoy. "The first drug for pulmonary hypertension was approved in 1995, although the disease was known since the early 1900s."

Raizada said that blood pressure is regulated by a hormonal system called the renin-angiotensin system. Too much of a key hormone in this system, angiotensin II, can raise [blood pressure](#). However, angiotensin II is balanced by two other hormones, ACE 2 and Ang-(1-7), that maintain normal cardiopulmonary pressure, according to previous research.

Their studies have shown that increasing the amount of these hormones in the body prevents pulmonary hypertension. But the researchers needed an effective way to deliver the hormones to test their therapeutic potential. Because the hormones are already found in the human body, Raizada said, they had little concern about potential side effects.

"All of the drugs on the market so far for hypertension and cardiovascular diseases are based on inhibiting angiotensin II and aren't very effective," Raizada said. "Many years ago, we began to question why the prevalence of hypertension and cardiopulmonary diseases does not decrease when you inhibit angiotensin II. Instead, we thought we should be targeting the hormones that balance angiotensin II."

Daniell studies protein drug delivery using plants and introduced genes with the ACE 2 and Ang-(1-7) proteins into plant chloroplasts of tobacco, which then could be grown, freeze-dried, enclosed in capsules and fed to rats. Plant cells protect protein drugs from acids and enzymes in the stomach, but drugs are released in the gut for absorption when bacteria in the gut digest plant cell walls. To make sure the proteins could travel across the intestinal wall and into the bloodstream, they were fused with a protein that binds to intestinal cells.

"The proteins we were dealing with are very large and unstable, only lasting a few minutes in the bloodstream when given as an injection," Daniell said. "We needed to find a way to stabilize the proteins to increase their lifespan in the bloodstream and make sure it was working the way we wanted it to."

When patients are treated with other medications, they typically see only a slight improvement—about a 10 percent reduction in pulmonary pressure. After the rats with established pulmonary hypertension had been treated with the medication for two weeks, their pulmonary pressure was reduced by 20 percent. After four weeks of using the plant-

delivered medication to treat a group of 8-10 rats with pulmonary hypertension, the researchers found that the medication reduced pulmonary pressure by 32 percent.

Though pulmonary hypertension causes vessels in the lungs to constrict, patients actually die from heart failure. But the drug also improved function on the right side of the heart, potentially avoiding heart failure in patients, Shenoy said.

Next, the researchers hope to test the drug in clinical trials.

"The bottom line is we have been able to find a revolutionary way to deliver a therapy through oral delivery for a disease which is in critical need for an immediate innovative therapy," Raizada said.

**More information:** "Oral Delivery of Angiotensin-Converting Enzyme 2 and Angiotensin-(1-7) Bioencapsulated in Plant Cells Attenuates Pulmonary Hypertension." *Hypertension*. 2014;HYPERTENSIONAHA.114.03871 published online before print September 15 2014, [DOI: 10.1161/HYPERTENSIONAHA.114.03871](https://doi.org/10.1161/HYPERTENSIONAHA.114.03871)

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