

# Researchers biosynthesize anti-cancer compound found in venomous Australian tree

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Stinging Tree in far north Queensland. Credit: Rainer Wunderlich, [CC BY-SA 3.0](#)

The Australian stinging tree (*Dendrocnide moroides*) is a plant that many

people avoid at all costs. The tree, which is a member of the nettle family, is covered in thin silicon needles laced with one of nature's most excruciating toxins, a compound called moroidin. "It's notorious for causing extreme pain, which lingers for a very long time," said Whitehead Institute Member Jing-Ke Weng.

There's another side to moroidin, though; in addition to causing pain, the compound binds to cells' cytoskeletons, preventing them from dividing, which makes moroidin a promising candidate for chemotherapy drugs.

Harvesting enough of the chemical to study has proven difficult, for obvious reasons. Now, in a paper published April 19 in the *Journal of the American Chemical Society*, Weng, who is also an associate professor of biology at the Massachusetts Institute of Technology (MIT) and former postdoc Roland Kersten, now an assistant professor at the University of Michigan College of Pharmacy, present the first published method to biosynthesize moroidin within the tissues of harmless plants such as tobacco, facilitating research on the compound's utility for cancer treatments.

## **Taking a leaf out of plants' book to create peptides**

Moroidin is a bicyclic peptide—a type of molecule made up of building blocks called amino acids and circularized to contain two connected rings. For synthetic chemists, moroidin has proved nearly impossible to synthesize due to its complex chemical structure. Weng and Kersten wanted to dig deeper into what methods the plants were using to create this molecule.

In plant cells, [cyclic peptides](#) are made from specific precursor proteins synthesized by the ribosome, the macromolecular machine that produces proteins by translating messenger RNAs. After leaving the ribosome, these precursor proteins are further processed by other enzymes in the

cell to give rise to the final cyclic peptides. In 2018, Weng and Kersten had elucidated the biosynthetic mechanism of another type of plant peptides called lyciumins, first found in the goji berry plant, which gave them some insight into how post-translational modifications might play a role in creating different types of plant peptide chemistry. "We learned a lot about the principal elements of this system by studying lyciumins," said Weng.

When they began to look into how moroidin was synthesized, the researchers found a few other plants, such as *Kerria japonica* and *Celosia argentea*, also produce peptides with similar chemistry to moroidin. "That really gave us the very critical insight that this is a new class of peptides," Weng said.

Weng and Kersten previously learned that the BURP domain, which is part of the precursor proteins for lyciumins and several other plant cyclic peptides, catalyzes key reactions involved in the peptide ring formation. They found that the BURP domain was present in the precursor proteins for moroidins in *Kerria japonica*, and seemed to be essential for creating the two-ring structure of the molecules. The BURP domain creates ring chemistry when in the presence of copper, and when the researchers incubated the moroidin precursor protein with copper chloride in the lab together with other downstream proteolytic enzymes, they were able to create moroidin-like peptides.

With this information, they were able to produce a variety of moroidin analogs in tobacco plants by transgenically expressing the moroidin precursor gene of *Kerria japonica* and varying the core motif sequence corresponding to moroidin peptides. "We show that you can produce the same moroidin chemistry in a different host plant," Weng said.

"Tobacco itself is easier to be farmed on a large scale, and we also think in the future we can derive a plant cell line from the existing tobacco cell lines that we put in the moroidin precursor peptide, then we can use the

cell line to produce the molecule, which really enables us to scale up for medicine production."

## Future use of moroidin

Moroidin's anti-cancer property is due, at least in part, to the compound's unique structure that allows it to bind to a protein called tubulin. Tubulin forms a skeletal system for living cells, and provides the means by which cells separate their chromosomes as they prepare to divide. Currently, two existing [anti-cancer drugs](#), vincristine and paclitaxel, work by binding tubulin. These two compounds are derived from plants as well (the Madagascar periwinkle and Pacific yew tree, respectively).

In their new work, Weng and Kersten synthesized a moroidin analog called celogentin C. They tested its anti-cancer activity against a human lung cancer cell line, and found that the compound was toxic to the cancer cells. Their new study also suggests potentially new anti-cancer mechanisms specific to this lung cancer cell line in addition to tubulin inhibition.

In the past, researchers have run into issues when trying to create effective drugs from peptides. "There are two major challenges for peptides as medicine," Weng said. "For one thing they are not very stable in vivo, and for another they are not very bioavailable and don't readily pass the membrane of a cell."

But cyclic peptides like moroidin and its analogs are a bit different. "These peptides essentially evolve to be drug-like," Weng said. "In the case of the Australian stinging tree, the peptides are present because the plants want to deter any animals that want to eat the leaves. So over millions of years of evolution these plants eventually figured out a way to construct these specific cyclic peptides that are stable, bioavailable and can get to the animal that is trying to eat the plants."

It's likely that the painful reaction that occurs when moroidin enters the body through a sting from the tree would not be an issue in traditional methods of administering chemotherapy. "The pain is really caused if you get injections of the compound into the skin," Weng said. "If you take it orally or intravenously, your body will most likely not sense the pain."

Somewhat counterintuitively, the compound could also be used as a pain reliever. "If something causes pain, you can sometimes use that as an anti-pain medicine," Weng said. "You could essentially exhaust the pain receptors, or if you alter the structure a little bit, you could turn an agonist into an antagonist and potentially block the pain."

On a more fundamental level, moroidin could help researchers study pain receptors. "We don't know exactly why being stung by the stinging tree produces that enormous amount of pain, and there may be additional pain receptors people haven't identified," Weng said. "Being able to synthesize moroidin provides a chemical probe that allows us to study this unknown pain perception in humans."

In the future, the researchers hope to create analogs of moroidin to study, and hopefully create an optimal version for use in cancer therapy. "We want to generate a library of moroidin-like peptides," Weng said. "We've done this for lyciumins, and since the initial moroidins are anti-tubulin molecules, we can use this system to find an improved version that binds to tubulin even tighter and contains other pharmacological properties making it suitable to be used as a therapeutic."

**More information:** Roland D. Kersten et al, Gene-Guided Discovery and Ribosomal Biosynthesis of Moroidin Peptides, *Journal of the American Chemical Society* (2022). [DOI: 10.1021/jacs.2c00014](https://doi.org/10.1021/jacs.2c00014)

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