Periwinkle can serve as tiny chemical plant

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MIT researchers have discovered a way to manipulate the chemistry taking place in the tiny periwinkle plant to produce novel compounds that could have pharmacological benefits.

"Plants are really nature's best chemists," says Sarah O'Connor, the Latham Family Career Development Assistant Professor of Chemistry and co-author of a paper on the work in the *Journal of the American Chemical Society*.

O'Connor and chemistry graduate student Elizabeth McCoy decided to explore the periwinkle plant in part because it is the only plant that produces vinblastine, a drug widely used to treat cancers such as Hodgkin's lymphoma.

The biochemical pathway that produces vinblastine and other alkaloid compounds is long and complicated, usually requiring at least 10 enzymatic steps, which occur in different parts of the periwinkle plant (also known as Catharanthus roseus).

O'Connor and McCoy essentially tricked the plants into producing new compounds by feeding them slightly altered versions of the normal starting materials (tryptamines) for alkaloid synthesis.

"You can make a great number of modifications of simple starting materials, and the plants incorporate those starting materials into the biosynthetic pathway," said O'Connor.

Alkaloids are believed to have a protective function for plants because they are toxic to bacteria and herbivores who try to eat the plants. This theory is bolstered by the fact that the reaction products move closer to the plant surface as they move through the biosynthetic pathway, said McCoy.

Vinblastine, which has been used as a cancer drug since the 1960s, is very difficult to isolate from the periwinkle plant because it is produced in minute quantities (the yield is about 0.002 percent of the plant's weight). However, it would be even more difficult (and expensive) to synthesize vinblastine in the laboratory.

"It's a beautiful and elegant synthesis, but it's not cost-effective, so industry does not currently use synthesis to make vinblastine," said O'Connor.

Other researchers are now running clinical trials for artificial analogues of vinblastine, so it could be beneficial if periwinkle plants could be induced to synthesize those same compounds or new compounds that might be even more effective.

Because it is easier to make modifications to the starting materials than the end product, the researchers' method could produce a diverse array of alkaloids to test for potential drug activity. "You can only make a limited number of modifications to natural products that are already synthesized," O'Connor said.

In their recent paper, the researchers describe 18 new products, but there are many more possibilities. "There's no end to what you could do to modify the starting materials," said McCoy.

Scientists often engineer bacteria and yeast to produce desired compounds, such as antibiotics, but few have tried it with plants, because

their biochemistry is so complex.

"Plants are the hardest to work with, so people have avoided looking at plant biosynthetic pathways," O'Connor said.

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