# Researchers uncover metabolic enzymes with 'widespread roles' in opium poppy

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University of Calgary scientists have discovered metabolic enzymes in the opium poppy that play "widespread roles" in enabling the plant to make painkilling morphine and codeine, and other important compounds. Credit: Riley Brandt, University of Calgary

University of Calgary scientists have discovered metabolic enzymes in the opium poppy that play "widespread roles" in enabling the plant to make painkilling morphine and codeine, and other important compounds.

The discovery, by university researcher Peter Facchini and PhD student Scott Farrow, includes the first biochemical reaction of its kind ever reported in plants, which may also occur in garden-variety poppies and other plants.

Their research, published this week as a cover story in the *Journal of Biological Chemistry*, sheds light on how the opium poppy – the world's only source of the valuable painkillers – evolved the ability to make morphine and other compounds.

"The functions of what we thought were really specific genes and enzymes involved in morphine biosynthesis are actually much broader," says Facchini, professor of biological sciences in the Faculty of Science and an internationally recognized expert on the opium poppy.

In 2010, Facchini's laboratory reported the discovery of two unique genes, and the enzymes they encode, that enable the opium poppy to synthesize morphine and codeine.

Enzymes are protein molecules – highly selective catalysts that accelerate both the rate and specificity of metabolic reactions.

The new finding shows that these enzymes in opium poppy, along with a third enzyme discovered by the U of C lab, "have these unexpected and widespread roles," Facchini says.

"There are more branches of related alkaloid metabolism that lead to a lot of different compounds that have different pharmacological and important biological properties in opium poppy."

The new insights could enable pharmaceutical companies to manipulate the biochemical pathway and create varieties of the opium poppy that produce higher levels of specific drugs, such as codeine or morphine, Facchini says.

Codeine is by far the most widely used opiate in the world and one of the most commonly used painkillers.

Codeine can be extracted directly from the opium poppy, although most of the painkiller is chemically synthesized from the much more abundant morphine found in the plant.

Canadians spend more than $100 million a year on codeine-containing pharmaceutical products and are among the world's top consumers of the drug per capita.

Facchini and Farrow suspect that the biochemical reactions they discovered also occur in garden-variety poppy species related to the opium poppy, as well as in other plants.

"The difference between related plants, in terms of their ability to make or not make morphine, might only be the activity of a single enzyme," Facchini notes.

If so, it may eventually be possible to manipulate metabolic pathways so that other plants – or even yeast and bacteria – can produce morphine, codeine or thebaine, an "intermediate" compound obtained only from opium poppy and used to make the painkiller drug oxycodone.

However, companies seeking to 'tweak' opium poppy biochemistry should be cautious, Facchini says, because the related metabolic pathways produce compounds with anti-microbial activity designed to protect the plant.

"If you're going to continue to rely on this plant as a 'drug-production system' and apply technological solutions to improving varieties, you better understand the biochemistry thoroughly," Facchini says.

Farrow spent the last three years unravelling the biochemical reactions, performing in vitro ('test tube') analysis on many compounds using state-of-the-art mass spectrometry equipment.

He also used a technique called virus-induced gene silencing to essentially knock out the genes' morphine- and codeine-making enzymes, which confirmed their widespread roles in the opium poppy's physiological functions.

Prior to this discovery, the only similar biochemical reaction reported in the scientific literature is a human enzyme that breaks down the illegal drug ecstasy, although the enzyme itself hasn't yet been identified.

Farrow is now investigating 20 other plant species genetically sequenced by Facchini's lab, to determine if the biochemical reaction also occurs in these plants.

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