Chemists discover cannabis 'pharma factory'

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Cannabinoids are produced on the flowers of the female plant of *Cannabis sativa* in tiny hair-like structures called trichomes, the plant's own "chemical factories." Credit: Jon Page (UofS/NRC), Klaus Adler (IPK-Gatersleben, Germany)

University of Saskatchewan researchers have discovered the chemical pathway that *Cannabis sativa* uses to create bioactive compounds called cannabinoids, paving the way for the development of marijuana varieties to produce pharmaceuticals or cannabinoid-free industrial hemp. The research appears online in the July 16 early edition of the *Proceedings of the National Academy of Sciences* (*PNAS*).

U of S adjunct professor of biology Jon Page explains that the pathway is an unusual one, involving a specialized version of one enzyme, called

hexanoyl-CoA synthetase, and another enzyme, called olivetolic acid cyclase (OAC), that has never before been seen in plants.

"What cannabis has done is take a rare fatty acid with a simple, six-carbon chain and use it as a building block to make something chemically complex and pharmacologically active," Page says.

Page led the research with PhD student Steve Gagne, who discovered OAC, and postdoctoral researcher Jake Stout, who discovered hexanoyl-CoA synthetase (reported earlier this year in *The Plant Journal*).

Cannabis has been cultivated for thousands of years for food, fibre, medicine and as a psychoactive drug. Cannabinoids such as delta-9-tetrahydrocannabinol, or THC, are produced on the flowers of the female plant in tiny hair-like structures called trichomes, the plant's own "chemical factories." The researchers used genomic analysis of isolated trichome cells to produce a catalog of the genes involved in cannabinoid production.

Page and his colleagues have already used the new enzymes to coax yeast to produce olivetolic acid, a key metabolic intermediate on the biochemical pathway that leads to cannabinoids.

"Now that we know the pathway, we could develop ways to produce cannabinoids with yeast or other microorganisms, which could be a valuable alternative to chemical synthesis for producing cannabinoids for the pharmaceutical industry," Page says.

There are more than 100 known cannabinoids, only a few of which have been explored for their possible medicinal uses. THC is the main psychoactive cannabinoid, responsible for the "high" sought by recreational users, as well as medicinal effects such as pain relief, nausea suppression and appetite stimulation. More than 19,000 patients in

Canada are authorized to legally use marijuana to benefit from these effects, and many others use cannabinoid-containing drugs via prescription. Another important cannabinoid, cannabidiol (CBD) has anti-anxiety and neuro-protective properties.

Page explains that knowledge of the cannabinoid-making pathway could also make matters easier for Canadian farmers. Plant breeders can now look for cannabis strains that lack key parts of the cannabinoid-making pathway, which would allow for zero-THC varieties (current Canadian regulations call for no more than 0.3 per cent THC for industrial hemp, compared to 15 per cent or higher in the more potent marijuana varieties).

Although hemp cultivation in Canada dates back to the 1600s in Quebec, today industrial hemp is a niche crop, grown mostly on the Prairies. Its popularity fluctuates considerably, with about 15,700 hectares (39,000 acres) grown in 2011 according to statistics from Health Canada, which regulates the crop.

While hemp is well-known as a fibre crop for everything from textiles, rope and paper, it is more often grown in Canada for its seed. Hemp seed, which is high in omega-3 and omega-6 fatty acids, is marketed for its healthy qualities. It is used in everything from lactose-free hemp milk, breakfast cereals, snack foods and protein supplements for athletes. Hemp oil is also used in cosmetic skin care products.

Provided by University of Saskatchewan