Cancer drug from rare plant in lab

Many of the drugs we take today to treat pain, fight cancer or thwart disease were originally identified in plants, some of which are endangered or hard to grow. In many cases, those plants are still the primary source of the drug.

Fig: *Podophyllum hexandrum* or Podophyllum commonly known as May apple is an herbaceous perennial plant in the family Berberidaceae

Scientists at Stanford University, California produced a common cancer drug -- previously only available from an endangered plant -- in a common laboratory plant. This work could lead to a more stable supply of the drug and allow scientists to manipulate that drug to make it even safer and more effective.

Stanford scientists have isolated the machinery for making a widely used cancer-fighting drug from an endangered plant. They then put that machinery into a common, easily grown laboratory plant, which was able to produce the chemical. The technique could potentially be applied to other plants and drugs, creating a less expensive and more stable source for those drugs.

The team used a novel technique to identify proteins that work together in a molecular assembly line to produce the cancer drug. They showed that the proteins could produce the compound outside the plant -- in this case, they had put the machinery in a different plant, but they hope to eventually produce the drug in yeast. Either the plant or yeast would provide a controlled laboratory environment for producing the drug.

Finding the machinery

The drug chosen by the researchers to focus on is produced by a leafy Himalayan plant called the mayapple (*Podophyllum hexandrum)*. Within the plant, a series of proteins work in a step-by-step fashion to churn out a chemical defense against predators. That chemical defense, after a few modifications in the lab, becomes a widely used cancer drug called etoposide.

The starting material for this chemical defense is a harmless molecule, podophyllotoxin commonly present in the leaf. When the plant senses an attack, it begins producing proteins that make up the assembly line. One by one, those proteins add a little chemical something here, subtract something there, and after a final molecular nip and tuck, the harmless starting material is transformed into a chemical defense.

The challenge was figuring out which of the many proteins found in the mayapple leaf were the ones involved in this pathway. Scientists started with the realization that the proteins they needed to find weren't always present in the leaf. It's only when the leaf is wounded that the molecule is made. And if the molecule is only made after wounding, the proteins that make that molecule are probably also only around after a wound as well.

It turns out that after damaging the plant leaf, 31 new proteins appeared. The team put various combinations of those proteins together until they eventually found 10 that made up the full assembly line. They put genes that make those 10 proteins into a common laboratory plant, and that plant began producing the chemical they were seeking.

Drugs from yeast

The scientists proven the molecular machinery works outside the plant, they put the proteins in yeast, which can be grown in large vats in the lab to better provide a stable source of drugs. Producing a drug in yeast also provides some flexibility that isn't present when isolating a drug from plants.

In yeast, scientists can modify the genes to produce proteins with slightly different functions. For example, they could nip a little more off the chemical or add a slightly bigger side chain, or subtly alter the function of the eventual drug. It may also be possible to feed the yeast a slightly different starting product, thereby changing the chemical that the molecular assembly line churns out. These approaches would provide a way of tweaking existing drugs in an effort to improve them.

This work could lead to new ways of modifying the natural pathways to produce derivative drugs that are safer or more effective than the natural source.

Journal Reference:

Warren Lau and Elizabeth S. Sattely. **Six enzymes from mayapple that complete the biosynthetic pathway to the etoposide aglycone**.*Science*, September 2015 DOI: 10.1126/science.aac7202