KU researchers close in on a natural compound to fight pancreatic cancer

Saffron compound crocetin may be effective against pancreatic cancer

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When it comes to drug discovery, Mother Nature's resources can't be beat. So says Shrikant Anant, PhD, associate director of The University of Kansas Cancer Center's cancer prevention and control program. He calls nature "the best combinatorial chemist," as the soil, forests and oceans contain a wealth of natural products that have evolved over millions of years into the most protective and least toxic compounds for plant survival.

Many of these compounds also exert interesting biological properties relevant to human disease. More than half of today's drugs originate, one way or another, from nature — "a classic example of reinventing the wheel," Anant says. Ancient Greeks and Egyptians knew that chewing willow tree bark would relieve fevers and pain; once chemistry came of age, scientists located and modified the bark's active ingredient, producing aspirin. Cholesterol-lowering statins were derived from the substance compactin, found in a type of fungus. And Taxol, one of the bigger anticancer drug success stories, has its roots in the yew tree.

For some time now, Anant has been working with Animesh Dhar, PhD, an associate professor in the University of Kansas Medical Center's department of cancer biology, to examine the effects of crocetin on pancreatic cancer, a deadly disease for which no effective therapies exist. Crocetin is a compound from saffron, a popular spice and food colorant and a key ingredient in many traditional Indian medicines. This collaboration recently received a $800,000 RO1 grant from the National Cancer Institute, a competitive award category that supports innovative research ideas from individual scientists.

"It's the first — and right now the only — NCI-funded grant investigating crocetin in cancer," Dhar says. He and his group estimate that they're less than a year from moving their research into a Phase I clinical trial.

To obtain federal funding, Dhar used preliminary data obtained from a KU cancer center-funded pilot study indicating that crude crocetin slows the growth of human pancreatic cancer cells grown either in a dish or as tumors under the skin of mice. Crocetin was also effective when combined with gemcitabine, a standard chemotherapy agent for pancreatic cancer. However, the order of this combination matters. When given concurrently, or when gemcitabine was given before crocetin, cancer cell growth was not affected; when Dhar and his team gave crocetin before gemcitabine, they saw a significant drop in the proliferation of pancreatic cancer cells.

Dhar points out another important observation: crocetin's effect on pancreatic cancer stem cells — that small yet deadly population of cells capable of dodging conventional chemotherapy. In the presence of crocetin, these cells are unable to form pinhead-sized round clumps, or spheroids, the most visible marker of their "stemness."

Dhar and Anant are now studying purified fractions from crude crocetin, which may have even more pronounced anticancer effects. They're collaborating with Gregory Reed, PhD, an associate professor in KUMC's department of pharmacology, toxicology and therapeutics, and William Gutheil, PhD, from the University of Missouri-Kansas City's department of pharmaceutical sciences. The group is particularly interested in crocetinic acid, one of these purified fractions.

"We're trying to find crocetin's most active constituents so we have a more potent compound that can be given at lower doses," Reed explains. "I'm helping to figure out crocetinic acid's effective dose as well as answers to other questions — for example, how crocetinic acid should be administered. Can it be given orally or does it have to be injected?"

Reed further illustrates this reductionist approach in making anticancer drugs out of natural products, citing a Phase I clinical trial that explored naturally occurring compounds in cruciferous vegetables — broccoli, cauliflower, cabbage and the like. "We found that when taken orally, one of these compounds caused changes correlating with a decrease in breast cancer risk," he says. "Whenever I talk about this, the question I get is 'How much broccoli do you have to eat?' Well, you'd be eating four to five pounds of it each day. That's why finding the active component and purifying it is far more practical."

Beyond figuring out crocetinic acid's pharmacological properties, Dhar and his colleagues hope to dissect its mechanism of action. They think interactions between crocetinic acid and the protein histone deacetylase 1 (HDAC1), which helps regulate the first step of gene expression, could play a role, because HDAC1 levels are elevated in pancreatic cancer.

Besides this focus on natural compounds, researchers are pursuing multiple other ways of tackling pancreatic cancer. While seemingly diffuse, "all these research roads will likely lead us to Rome," Anant says, "by which I mean we'll eventually learn the best ways to combine different therapies at lower doses, so treatments are less toxic and cancer cells don't become resistant to any one

treatment." But it's a highly complex process, he adds, as two people with the same cancer don't necessarily have the same molecular pathways activated or disrupted.

Anant reckons tumorgrafts — where scientists transfer snippets of human tumor tissue directly into mice — could prove useful for testing new therapy combinations. Tumorgraft-bearing mice get slammed with assorted cocktails of drugs, allowing scientists to learn which drug combinations work and which don't. According to Anant, it usually takes just 15 days to obtain these results.

Anant, Dhar and collaborators at KUMC are now developing a protocol to test drug candidates derived from natural compounds — including crocetinic acid — against mice carrying pancreatic tumorgrafts. This, Dhar says, should give them the preclinical data they need to make a Phase I clinical trial on crocetinic acid feasible.

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