Behind the Scenes in Pharmacognosy

Recently, the Journal of Natural Products *published an article from the laboratory of ASP members Drs. Dale Nagle and Yu-Dong Zhou at the National Center for Natural Products Research, School of Pharmacy, University of Mississippi (UM), Oxford, Mississippi. The article, "Toxins in Botanical Dietary Supplements: Blue Cohosh Components Disrupt Cellular Respiration and Mitochondrial Membrane Potential," details innovative work detecting the impact of blue cohosh on mitochondrial function. We appreciate Dr. Nagle taking the time to describe his laboratory's work in more detail. Please read the online article at* J. Nat. Prod.*, 2014, 77, 111-117.doi:10.1021/np400758t.*

By Dr. Amy Keller

Dr. Dale G. Nagle (left) and Dr. Yu-Dong Zhou (right).

MS. TAYLOR BRYAN

How did you choose your original set of plants for the ability to interfere with cellular respiration? Is there a certain type of toxicity you looked for prior to screening?

The major focus of our current research is the discovery of molecular-targeted antitumor and antimetastatic natural products that inhibit organ-specific secondary tumors. Screening plant extracts for activities that suppress hypoxia-induced gene expression led to the discovery that certain plant metabolites exhibit potential antitumor activity, and these extracts contain compounds that disrupt mitochondria-mediated cellular signaling. Therefore, we began to examine plants used as herbal medicines for the ability to potentially produce organ toxicity by acting as mitochondrial disruptors. In cell-based assays, blue cohosh (*Caulophyllum thalictroides*) extract caused a rapid burst in respiratory rate, followed by a dramatic decrease in cellular oxygen consumption. These results and previous reports of blue cohosh-associated idiosyncratic organ toxicities lead our team to characterize the mitochondria toxic constituents of blue cohosh.

Who in your laboratory carried out the research?

Our mitochondria-induced herbal toxicity project is a collaborative research effort between our group, Dr. Zulfiqar Ali and Dr. Ikhlas A. Khan, both at the National Center for Natural Products Research at the School of Pharmacy, UM, Oxford, Mississippi, and Dr. Mika B. Jekabsons, Department of Biology, UM. My former PhD student, Dr. Sandipan Datta, and Dr. Zhou's technician, Ms. Fakhri Mahdi, conducted the mitochondrial respiration and cell viability studies.

Would you provide a brief explanation of the work and results in your own words?

Mitochondrial poisons can produce reactive oxygen species (ROS)-mediated liver and cardiac toxicological events. In most cases, mitochondrial manganese-superoxide dismutase (MnSOD) and other protective antioxidant systems are believed to preclude the occurrence of toxicological events in preclinical models and initial small-scale clinical studies. However, rare idiosyncratic toxicological events begin to appear when large populations use mitochondria-toxic agents. Drug-induced mitochondrial dysfunction has forced the withdrawal of major pharmaceuticals like troglitazone and is responsible for about half of the hepatotoxicity and cardiotoxicity-associ-

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ated Food and Drug Administration (FDA) black box warnings on approved drugs. It is for this reason that we began working with Dr. Khan and his group in the UM National Center for Natural Products Research to examine a panel of over three hundred extracts from plants used in traditional Chinese, Ayurvedic, and Western Herbal Medicine for their ability to disrupt cellular respiration. In the United States, some midwives use blue cohosh to induce labor. However, the use of blue cohosh has been associated with organ injury, myocardial infarction, and other complications. Extracts of blue cohosh and purified cauloside-type saponins were found to impair mitochondrial function by disrupting membrane integrity.

You successfully characterize the mitochondrial toxicity of blue cohosh. How widespread do you think this toxicity is in natural products? Do you expect this to preclude the usage of many botanicals?

To our surprise, initial evaluation of extracts from plants used in herbal medicine indicated that as many as 5% of a representative botanical sample set contained compounds that either inhibited mitochondrial electron transport, acted as protonophores that uncouple mitochondrial proton gradients, or directly disrupted cytoplasmic and mitochondrial membranes. We believe that once identified, these mitochondrial disruptors will provide a mechanistic basis for future toxicological studies and yield toxicological markers for botanical dietary supplement analysis and quality control.

What is a favorite nonscientific activity of your lab?

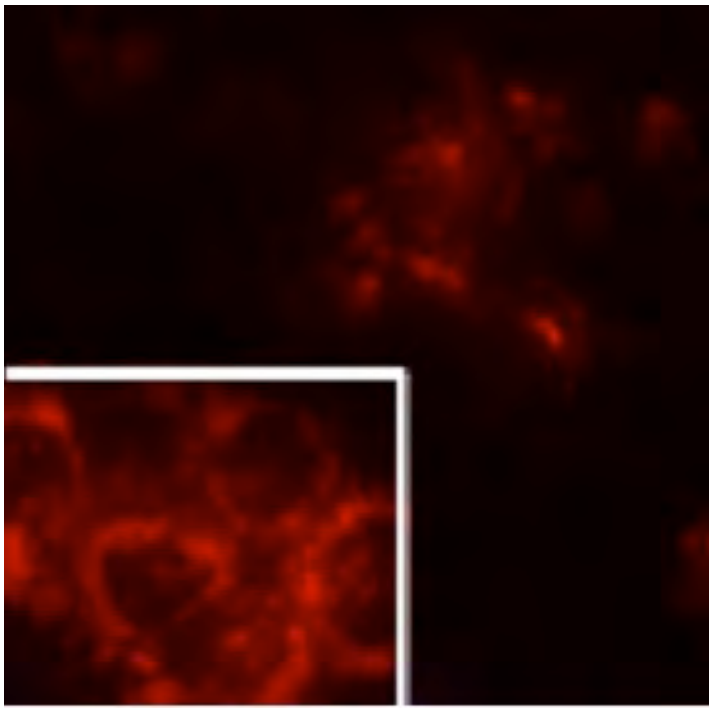
Our long-term collaborative research program is a combination of my natural products drug discovery efforts and Dr. Yu-Dong Zhou's molecular and cell biology research. As a 'research couple,' our most important and time-consuming nonscientific activity is raising our two children, Alexandra and Nicholas.

What is your lab's motto or slogan?

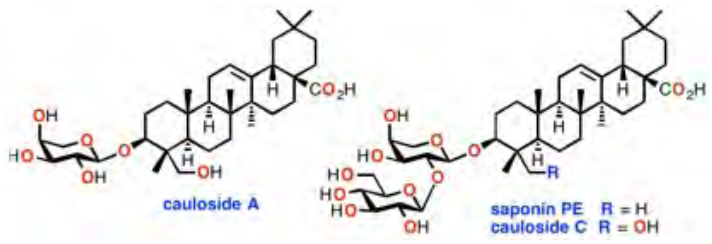
If we have a lab motto, it would be something like "In both research and life, never be afraid to try strange things, follow unexpected results, or go towards completely new directions."

What is your greatest extravagance in the lab?

Because we work and raise our children together, the greatest extravagance for Yu-Dong and I is our love of travel and the involvement of our children in our science-related adventures. Both children have grown up around conferences, including American Society of Pharmacognosy Annual Meetings. Ever since they were small, they have been exposed to natural product research and have made friends with the children of other scientists. Many of our colleagues often come up and tell us that they have witnessed how quickly the children are growing. While it sometimes represents a tremendous personal expense, both Yu-Dong and I believe that including our children in our work-related travel provides them with an invaluable opportunity to see the world, experience other cultures, and better appreciate professional and academic life (and life in general). ■



Mitochondrial membrane potential disruption in T47D breast tumor cells by saponin PE. Cells were loaded with TMRM+ dye to visualize membrane potential and exposed to saponin PE. Image before saponin PE addition is shown as an insert inside the panel.



Compound: Mitochondria toxic cauloside-type saponins from blue cohosh.