
Specialty Crops and Human Health Impacts

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I am from the North Carolina Research Campus, which is devoted to nutrition, agriculture, biotechnology and functional food. Scientists from seven universities on this campus are focused on specialty crops that provide bioactive compounds, which, when you ingest them or put them on your skin topically, they interface with human therapeutic targets to counteract chronic disease or bolster metabolism to increase endurance. These are the crops that your grandmother said you should eat, and maybe you didn't because you didn't like vegetables. We are going beyond what grandma said, going beyond anecdotal evidence to try to elucidate biomarkers: what are the mechanisms of action of compounds in specialty crops that help them to interact with human therapeutic targets and counteract disease? What are these bioactive phytochemicals or "phytoactives" (Figure 1)?

Not all phytochemicals are important for human health, but phytoactives are those that bolster human health in some way, and many are present in specialty crops.

It's important to note that phytoactives are not necessarily plant nutrients. Of course, specialty crops contain nutrients as well: minerals, vitamins, *etc.*, that build strong bones and teeth. The phytoactives tend to be secondary compounds, not necessary for the plant to grow but which help human metabolism. They include pigments, anthocyanins, betalains, chlorophylls and carotenoids, which provides a convenient message for consumers: "Put some color on your plate. Don't just eat foods that are brown and white." When you do put color on your plate, you tend to be consuming phytoactive compounds, which are associated with pigments in many specialty crops. Concentrations and profiles of phytoactives vary with species and variety. Some sources are richer than others and some are more efficacious against certain disease conditions than others, but they are all there.



Figure 1. Bioactive phytochemicals—“phytoactives”—are natural compounds in fruits, vegetables, nuts and grains that positively affect human health.

At the Plants for Human Health Institute on the North Carolina Research Campus, we are investigating the gamut, from whole foods to functional foods to phytopharmaceuticals, *i.e.* removing and purifying an active compound from a plant and putting it into a pill, like a pharmaceutical. However, our major focus is on whole foods derived from specialty crops. For this presentation, I will address four questions:

- Why the Current Attention?
- How do Phytoactives Modulate Human Health?
- Can Genomics, Metabolomics, *etc.*, Pinpoint How Phytoactives Work?
- What’s the Reaction in the Marketplace?

WHY THE CURRENT ATTENTION?

You can hardly open a general-interest magazine or the popular section of a newspaper without finding something on functional foods. After Oprah Winfrey said that she “pops” blueberries like M&Ms during the day, sales of blueberries went through the roof. I talk about berries a lot because that’s my area of research, and, inevitably, the talk-show host will say, “This is wonderful, but why are we learning about it only now?” In fact, we are not just learning about it today. This is ancient stuff. Traditional ecological knowledge includes a lot on specialty crops—not named as such, of course—and their impacts on health: fruits, vegetables, spices, herbs, *etc.* The science hasn’t been behind them until now, and with the tools we have today, we are able to characterize the compounds involved. With animal models and clinical trials, we can determine how phytoactives interact in the human body, clearance times and locations of accumulation. We finally have the tools to investigate how these things are working.

To make the jump from traditional ecological knowledge to science now, it's important to realize why plants synthesize these compounds. Usually they are produced in response to environmental stress. We like to say "stressed for success" because plants, being sessile, need a cornucopia of chemical defenses against disease, insect infestation, nematode attacks, UV light, and so on. They need those defenses to survive, and they are the same compounds that, when we ingest them, counteract chronic disease.

HOW DO PHYTOACTIVES MODULATE HUMAN HEALTH?

How do phytoactives modulate human health, whether it be from a pharmaceutical, cosmeceutical or functional food standpoint? It would be advantageous if functional foods or wild plants that have phytoactive compounds acted like pharmaceuticals, with a nice bridge between using a plant to protect your health and using a pill to protect your health. But, plants don't work like that. They contain complex, interacting mixtures of compounds each of which may potentiate effects in the human body. It's hard to sort out the multiplicity of bioactivities. The compounds can do a number of different things. They might have activities against cancer and the same little group of compounds may be active also against cardiovascular disease. It's tough for doctors and scientists to understand, tending to mitigate against using specialty crops in medical treatments.

CAN 'OMICS PINPOINT HOW PHYTOACTIVES WORK?

With a pharmaceutical, you have a single active compound in a pill, facilitating dose-response and human efficacy tests. But when it's a plant extract and you tease out the components and pick out an active fraction via some activity in a bioassay, a lot of times when you purify the compound, you lose the activity. What's going on? A lot of times with plants, a synergistic effect of a potentiating compound on an active compound results in the "big bang" for human health. So there may be a multiplicity of bioactivities; blueberry is a good example. Positive effects on urinary tract infections have been attributed to blueberries—much like to cranberries—as well as beneficial effects on cardiovascular, optic, cancer and brain-function problems.

On the other hand, skepticism exists on the part of doctors, because they need to understand the biomarkers and see the proof. So, "omics" is one way to provide proof. We are starting to use genomics, transcriptomics, proteomics and, especially, metabolomics. If you have those tools in your hand, you can do a lot to decipher how active compounds are working, to pinpoint biomarkers.

We have a blueberry-genome sequencing effort that will be completed by the end of summer 2013. It's a complicated genome that no one else wanted to tackle. The database will be open to people looking at cranberry and other plants in the genus *Vaccinium*. Knowing the genomics leads to understanding activities within the human body.

The launch of the Plant Pathways Elucidation Project ("P-Squared EP") is planned for June 2013. North Carolina State and the University of North Carolina-Charlotte will be academic partners. At NC State we will handle the biology whereas Charlotte will handle bioinformatics; the biological data that we generate will go into a knowledge-based cloud over the whole project to feed information into what a plant makes, how it makes it,

what's the pathway it takes to get there, and, finally what good the product is for human health. In building this knowledge base, Dole and General Mills will be industry partners and Castle & Cooke will be a sponsor. Developed technologies will help us to understand how specialty crops contribute to human health; can we quantify it so that it's validated in every way?

General Mills and Dole have opened their files on pathways they have elucidated for oat, pineapple, and berries, and they are looking to the university researchers to pull together teams for complex pathway analyses. We will initiate the effort in two weeks, focusing on four crops with input from our industry partners: oat (*Avena sativa*), broccoli (*Brassica oleracea*), strawberry (*Fragaria x ananassa*) and blueberry (*Vaccinium* spp.). Five newly recruited PhD students will start on June 10, 2013, each of whom will supervise six undergraduate summer interns to put together pathways. Almost \$1 million have been provided by the UNC general administration to jumpstart the effort and to ensure that the PhD students will have funding for four years. It's exciting to get this going because it involves tools that we already had but we needed manpower to put them to work to generate useful data. Several local junior colleges and schools in the UNC system are donating interns. We will not donate any, but we will pay the interns to work intensively with the PhD students as teams.

Clinical Trials

Another example of how we get to the bottom of how specialty crops work is with clinical trials. These have always been horribly expensive, which is why they have not been used to investigate specialty crops or functional foods. We are fortunate to be partnering with the Appalachian State University and members of their human performance laboratory where they do clinicals, many with athletes—runners, cyclists, NASCAR pit crews, *etc.*—looking at the effects of functional-food components on exercise performance. For example we have done some work with runners, supplementing their diets with blueberries and green tea to see the effects of polyphenolics on classic markers of inflammation and oxidative stress using metabolomics. Classically you don't see oxidative stress or inflammation changes in highly trained athletes, but a nice thing about athletes is that they will cooperate if they think that the process will improve their performance and make them stronger. You don't have to pay them as much as for a normal clinical trial and they permit biopsies.

After consuming a supplement of blueberry green tea for 14 days, athletes were exposed to periods of intensive exercise, sufficient to induce oxidative stress (Figure 2). Only insignificant differences between the placebo and treatment groups were seen in the gross markers of oxidative stress like C-reactive protein. But we did see differences in bioavailability. The athletes who were supplemented had excellent profiles of gut bacteria metabolism of phenolic phytochemicals. We saw, for the first time, that compounds from blueberry and green tea were actually getting into the blood of the athletes, intensified by kind of a gut leakiness with intensive exercise which persisted during the recovery period, so that bioavailability was intensified as revealed by the polyphenolic signature. Gut microbial metabolism of the plant polyphenols was clear in the treatment group versus the placebo group. Furthermore, runners who were supplemented with blueberry

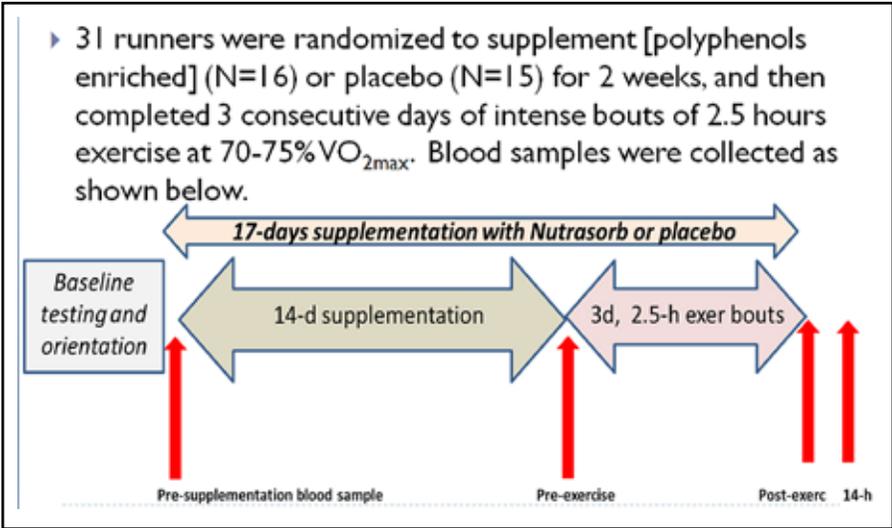


Figure 2. What are the effects of phytoactives on athletic performance?

green tea protein continued to utilize fatty acids—they had higher ketogenesis—during the recovery period. Athletes show a burst in oxidative stress and fat burning while they are exercising, but, whereas the placebo group went down to normal levels during the 14-hour recovery period, fat burning continued in the treatment group, which was quantifiable using metabolomics.

REACTION IN THE MARKETPLACE

Wild blueberries have been harvested commercially for many years in Maine and the maritime provinces of Canada; it's backbreaking work (Figure 3). Although it was the second largest industry in Maine, it was not highly lucrative for farmers until, in 1998, the "antioxidant" message emerged (Figure 4).

This wild blueberry antioxidant message was confirmed by researchers in Canada and the United States, and later in Europe. A lot of work has been done on wild blueberries and diabetes and obesity. Data from clinical trials at the Pennington Biomedical Research Center are conclusive for efficacy of blueberries for increasing satiety in their patients and cutting triglyceride levels. For hyperglycemia—the hallmark of diabetes—wild blueberries did better than metformin, the drug of choice for diabetes; blood-glucose levels were reduced in six hours. These and similar data attracted much media attention.

In 1999, colleagues at Tufts University, Barbara Shukett-Hale and James Joseph, showed that inclusion of blueberries at 2 percent of the diet alleviated or prevented the symptoms of dementia in artificially aged rats. Furthermore, losses in cognitive and motor function were partially replenished by introduction of the blueberry diet. This and similar research, reported in the mass media, have taken the humble blueberry from an addition to muf-



Figure 3. Labor-intensive harvesting of wild blueberries in Maine.

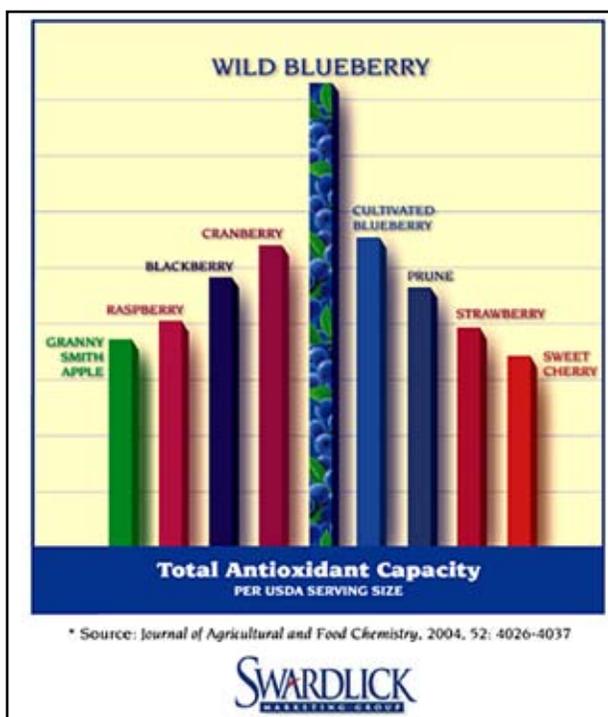


Figure 4. Nature's #1 antioxidant fruit.

finds to a health icon. These days, it's hard to pick up a health-related magazine without finding something about blueberries in particular. Other functional foods from specialty crops have benefitted in the same way, because people are turned on to what they can do proactively for their health.

Figure 5 shows increased production of cultivated and wild blueberries since 1998 when news of positive health effects first made the headlines.

We know what we're supposed to eat and we know how much we're supposed to eat. However, it's estimated that approximately 1 percent of the American public—including educated people—actually eats the amount of fruits and vegetables they're supposed to eat. There are many reasons why people don't do what they're supposed to do. How do we take bioactives from fruits and vegetables, from specialty crops, and get them in a shelf-stable, convenient form to more people?

We are working with the US Army to develop ways of getting fruits and vegetables to soldiers in the field. Figure 6 shows shelf-stable, low-sugar protein-rich flours containing extract from muscadine grapes. The same can be done with kale extract. The preparations are stable for over three years in some cases. Soldiers in the field will eat it because it tastes good, it's nutty, and they don't care if it's GMO or not.



Figure 5. Blueberry production trend ($\times 10^6$ pounds/year).

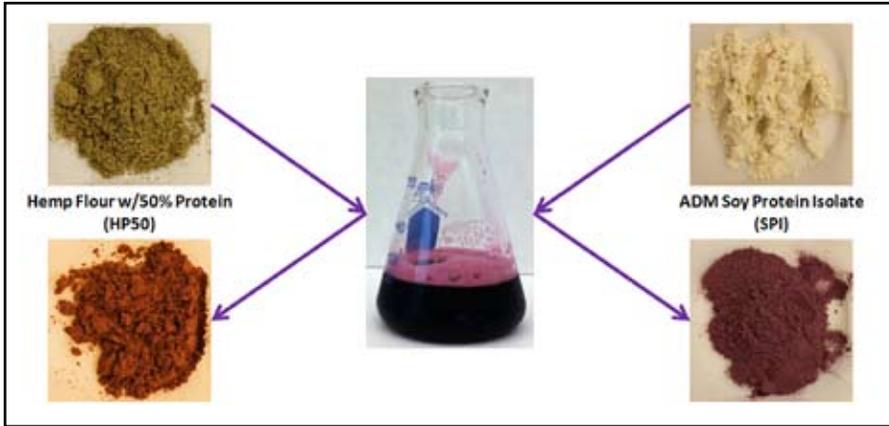


Figure 6. One-step sorption of the medium polarity polyphenolics in muscadine juice, free of unwanted/non-nutritional material.



MARY ANN LILA is director of the Plants for Human Health Institute (PHHI) at North Carolina State University on the NC Research Campus. She holds the endowed David H. Murdock chair, and is a professor in the Department of Food, Bioprocessing, and Nutrition Sciences. Through transdisciplinary discovery and outreach, the team at the PHHI is pioneering a dramatic shift in the way the American public views and uses food crops, not merely as a source of nutrients and flavorful calories, but as sources of powerful components that protect and enhance human health. Her research team focuses on wild and domesticated berries and their wide-ranging health benefits, including alleviation of the symptoms of diabetes and metabolic syndrome. Current efforts include a Bill & Melinda Gates Foundation Grand Exploration Challenges project in Zambia and projects in Egypt, Central Asia, Oceania, Mexico, Ecuador, Chile, subSaharan Africa and New Zealand.

Formerly (2006–2008), she was director of ACES Global Connect (the international arm of the College of Agriculture, Consumer and Environmental Sciences at the University of Illinois) and associate director of the Functional Foods for Health Program (1997–2000) at the University of Illinois. She is vice president of the Global Institute for BioExploration, an R&D network that promotes ethical, natural product-based pharmacological bioexploration to benefit human health and the environment in developing countries.