LESLIE GUNATILAKA

The biomass of *Withania*, a medicinal plant, is about five times greater in aeroponically-grown plants, as noted in the contrasting leaf sizes above.

A New Anticancer Compound From An Ancient Plant

Using a different agricultural method leads to discovery

By Susan McGinley

The powdered roots and/or extracts derived from roots of the winter cherry plant—*Withania somnifera* (L.) Dunal—have been used for more than 3,000 years in India as a general tonic to build stamina, improve mental concentration, relieve stress and enhance health.

Commonly known as "ashwagandha" in Ayurvedic medicine, scientific tests on the preparation have shown that it has anti-inflammatory, cardio-protective, antioxidant and antitumor properties, among others.

The compound withaferin A, scientifically studied since the 1960s, seems to play the largest role in the plant's anticancer effects by reducing tumor mass and preventing the growth of blood vessels that make a tumor malignant. It also shows promise in treating Alzheimer's and Parkinson's diseases.

At the University of Arizona, scientists in the Southwest Center for Natural Products Research and Commercialization (Natural Products Center) in collaboration with the Whitehead Institute at the Massachusetts Institute of Technology, have discovered a second form of withaferin that has identical functions in a less potent, slower-acting form that might be used as a "prodrug," or drug precursor in the pharmaceutical industry.

"Finding a water-soluble analog of withaferin A in this medicinal

THE SOUTHWEST CENTER FOR NATURAL PRODUCTS RESEARCH AND COMMERCIALIZATION (SCNPRC)

Scientists at the Southwest Center for Natural Products Research and Commercialization are working with universities, with agrochemical and pharmaceutical companies, and with other commercial entities to develop new biological and industrial products. Many of the SCNPRC's projects aim to improve the longevity of agriculture in Arizona, the Southwest, and semiarid lands throughout the world, and to understand the complex ecology of arid land ecosystems. As part of the Office of Arid Lands Studies, the SCNPRC recently joined the School of Natural Resources and the Environment in the University of Arizona's College of Agriculture and Life Sciences.

plant that is readily converted into its biologically active form under physiological conditions is significant," says Leslie Gunatilaka, director of the SCNPRC, "especially if it turns out to be a clinically useful drug."

Withania is widely cultivated for commercial use in its native India, and also in the Middle East and in North America. Ashwagandha is sold as a dietary supplement in the United States and Europe. Although traditionally grown outdoors in soil, the UA team decided to use an entirely nontraditional method—aeroponics—to produce bulk amounts of withaferin A needed for biological evaluation.

"We found that the biomass of *Withania* is about five times greater in aeroponically-grown plants," says Gunatilaka. In aeroponics, plants are set over enclosed chambers where their suspended roots are misted with water and nutrients, instead of growing in soil.

"Using the aeroponic system for cultivation, we've been able to produce over 20 grams of withaferin A in a single greenhouse operation in Tucson," he says. "It would normally cost around $195 just for 10 milligrams. And although *Withania* usually takes two to three years to mature to sizeable roots to be commercially viable, here it takes just six to nine months."

The UA College of Agriculture and Life Sciences provided funding for the project, along with the USDA. In addition to Gunatilaka, the research scientists included Ya-ming Xu, Marilyn T. Marron, Emily Seddon and Stephen P. McLaughlin, Natural Products Center; Dennis Ray, UA School of Plant Sciences; and Luke Whitesell, Whitehead Institute.

Not only did the aeroponic method yield bigger plants faster, with more withaferin A than usual, it also unexpectedly stimulated the plants to produce large amounts of a new natural product—a water soluble sulfate form of withaferin A.

Upon testing, this new form demonstrated the same bioactivity as withaferin A. It was able to inhibit the proliferation and survival of tumor cells, disrupt tumor formation and induce the healthy cells' heat-shock response to reduce stress and increase survival, according to the researchers.

The difference is that the sulfate form of withaferin A is slower acting and water soluble, and can be converted to withaferin A in cell culture media. The researchers, expecting that this withaferin A analog will convert to its active form when metabolized in the body, are pursuing further testing in animal models. The patent will be held by the UA and MIT.

Withaferin A is just one of hundreds of such compounds the Natural Products Center has isolated, characterized and evaluated since its inception in 1996. The center searches for compounds in desert plants and their associated microorganisms that can improve human health and also be developed as potential industrial products in Arizona. So far, Natural Products Center scientists have discovered several compounds in desert organisms that can significantly inhibit the growth of tumors. Many have been patented and have progressed to extended evaluation for their pharmaceutical value. ✪

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