

The Neuroprotective Benefits Of Plant-Cell-Cultivated Saffron

Interview by Sheldon Baker

Weslee Glenn, PhD, is the vice president of innovation at Ayana Bio, spearheading the company's R&D and commercialization efforts designing cellular technology to produce plant natural products. Formerly Provivi's director of metabolic engineering, his expertise lies in engineering biocatalysts and pathways to produce valuable bioactives for health and wellness. Glenn earned his PhD and Postdoctoral at MIT and Caltech.

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Integrative Medicine: A Clinician's Journal (IMCJ): The NIH awarded Ayana Bio a grant to research the neuroprotective benefits of plant-cell-cultivated saffron. What do you hope your studies will show?

Weslee Glenn, PhD: First, we hope to understand the levers that drive production of health-promoting molecules from *Crocus sativus* L ("saffron"). The biosynthesis of these molecules has been worked out for the most part. But comparatively little is known about what regulates their biosynthesis (what causes *C. sativus* cells to produce these molecules). Understanding regulation will help us increase the cell culture's productivity. Second, we hope to identify a complex of saffron bioactives that demonstrates neuroprotective benefits for Huntington's disease. Ultimately, we hope our research shows how plant cell-cultivated saffron can yield enhanced levels of neuroprotective compounds found in traditionally grown saffron. Huntington's disease is the focus of this study, but the work outlined here could inform other potential health benefits of saffron as well.

IMCJ: Why focus on saffron?

Dr. Glenn: Like many other botanical ingredients, saffron faces a complex and uncertain future in the face of climate change. While the medicinal properties of saffron have long been touted, its limited supply has driven up costs and made it difficult to conduct comprehensive research

studies. Further, the plant requires labor-intensive harvesting practices, often taking 170 000 flowers to produce just one kilo of saffron. These factors make high-quality saffron an expensive ingredient for health and wellness products.

IMCJ: How do current saffron supplement ingredients differ from what your plant-cell-cultivated ingredient will offer?

Dr. Glenn: Saffron's high cost makes it a prime target for adulteration. I'm certainly not calling out any one company or product because the problem is so pervasive. But plant cell cultivation is a solution that will allow us to produce high-quality products consistently.

IMCJ: Further explain Ayana Bio's plant cell cultivation.

Dr. Glenn: We coax cells from plant parts like leaves and shoots into reentering the cell cycle. This process forms a largely unorganized cell mass called a callus. From these cells, we create a liquid culture that we test against a variety of growth and process conditions to understand how these variables impact productivity. We then scale up the top cell line, medium, and process groupings. This process is similar to brewing beer, but with plant cells and oxygen instead of yeast (or bacteria) and anaerobic conditions. By providing these plant cells with carbon and nitrogen sources, oxygen, vitamins, and minerals, Ayana Bio produces plant biomass without needing to grow the entire plant. A few weeks later, the plant cell line is fully propagated and ready to harvest as an ingredient for health and wellness products.

To give an example, if you cultivated blueberry plant cells, the end product would look nothing like a soil-grown blueberry but would retain the health beneficial molecules found in the berry. The same is true for saffron. Our product won't look like saffron threads but will have all the health-beneficial molecules.

IMCJ: What health benefits have previous saffron studies shown?

Dr. Glenn: Clinical studies demonstrate that saffron improves defense against oxidative stress, which slows the progression of neurodegenerative diseases such as

Alzheimer's disease. Studies have also shown saffron's ability to improve depressive symptoms, aid in weight loss by increasing satiety, and treat age-related macular degeneration by preserving multifocal electroretinogram responses, making it a powerful health ingredient with interconnected benefits.

IMCJ: What are the company's capabilities to explore simultaneous cell lines?

Dr. Glenn: Ayana Bio uses machine learning to analyze hundreds of plant cell lines simultaneously for the most promising starting points. This information rich approach allows us to find, create, and scale complex plant molecules for industries like food and beverage and cosmetics that depend on the highest-quality ingredients. In contrast, other companies seem to focus on one cell line and a few conditions at a time.

Ayana Bio uses high throughput synthetic biology capabilities like sequencing, omics technology, and analytical chemistry to select the best plant cell lines at a massive speed and scale. Transcriptomics and metabolomics workflows are our bread and butter, meaning we monitor the genes being turned on or off and the molecules inside our cells under hundreds of different conditions. Metabolomics and transcriptomics datasets are interesting and informative alone, but we gather even greater insights by correlating them with machine learning. Ultimately, machine learning helps us predict and control how our plant cells will respond to different treatments, which helps shorten the development timeline.

IMCJ: Ayana Bio has created a Plant Cell Advantage (TM) portfolio that leverages plant bioactives. Do you consider plant-cell cultivation a trend?

Dr. Glenn: No. The foundational studies of plant cell cultivation were published over 60 years ago. So, I'd say

that plant cell cultivation has been a long time coming. But key aspects still need to be worked out. As a pioneer in the industry, we aim to foster widespread positive understanding of the numerous benefits of plant cell cultivation, from enhancing the nutritional content of consumer products to taking the strain off traditional agricultural supply chains.

IMCJ: Will plant-cell-derived saffron be offered globally?

Dr. Glenn: We are currently in the process of exploring and optimizing our saffron cell line, medium and process grouping. After that, we will scale the production of plant cell-derived saffron, complete our pre-clinical studies, and find customers to continue building the market.

