Exhibit FF

Science 101

What is Pterostilbene?

This potent polyphenol is promising in health and aging research because of its molecular structure and bioavailability. But it might be able to do more than we even know.

In 2003, researchers gave red wine drinkers everywhere reason to raise a glass when they announced that resveratrol — a natural chemical found in, among other things, grape skins — might be linked to long life.

Resveratrol, they found, extended the life span of yeast cells by as much as 70 percent. Plus, it seemed to induce gene expression changes that gave them reason to believe the compound might prevent and treat a wide-range of age-related diseases, including diabetes, heart disease, cancer, and Alzheimer's.

Researchers have pinned their hopes on a new rising star called pterostilbene (pronounced tear-oh-STILL-bean).

But 15 years and thousands of scientific studies later, and resveratrol hasn't lived up to its initial promise. The trouble is, it disappears from the body in roughly 15 minutes — meaning, in scientific terms, it isn't very bioavailable.

So researchers have pinned their hopes on a new rising star called pterostilbene (pronounced tear-oh-STILL-bean), which is very similar to resveratrol but with one tiny but crucial structural difference: It has just one hydroxyl group, compared to resveratrol's three. Hydroxyl groups facilitate metabolization (the way to get rid of the molecule) by the body. Fewer hydroxyl groups make it harder for the body to eliminate the molecule — no bad thing when the molecule has benefits. The upshot is that pterostilbene's slightly different molecular structure allows it to cross cell membranes more easily and hang out in the body longer than resveratrol.

"Resveratrol was like the poster child for polyphenols," says Ryan Dellinger, Elysium's director of scientific affairs whose doctoral research involved pterostilbene. There is no great reason for this: Dellinger thinks it's likely because, with limited money and time for scientific research (and more than 500 "promising" polyphenols to study), companies and scientists focused on the one that —at the time— seemed the most promising.

One good thing: Pretty much everything you know about resveratrol is true for pterostilbene, Dellinger says. Only it's more potent.

How Pterostilbene Works

Pterostilbene is a polyphenol, a type of molecule that occurs in plants, particularly small berries and nuts. Blueberries are a particularly rich source of pterostilbene; although it

is found in grapes, pterostilbene (unlike its cousin resveratrol) doesn't survive the wine-making process.

What's a polyphenol? "Phenol" refers to a certain chemical structure (in this case, a hydroxyl group linked to a benzene ring); "poly" just means the molecules have more than one of the structure. One of polyphenols' main jobs is to help the plant fight off pathogens. When eaten by humans, polyphenols may serve as powerful antioxidants, which can stop or delay damage to cells.

Scientists have been aware of phenols since the early 19th century — Joseph Lister, the pioneer of antiseptic surgery, reported on one phenol's disinfectant properties in 1867 — though the term "polyphenol" didn't have its first recorded use until 1894.

As with the rest of polyphenols, researchers don't fully understand how pterostilbene works. Dr. Jose M. Estrela, a professor of physiology at the University of Valencia (Spain) who has studied pterostilbene's anti-cancer properties, says that in the lab, one can incubate cancer cells (for example, a human skin cancer cell) in culture flasks in the presence of pterostilbene (at a concentration that can be achieved in blood or tissues of a living experimental animal, such as a mouse) and see zero effect. But administer it intravenously to a tumor-bearing mouse, and you'll see some inhibition of the cancer. How is that possible? The hypothesis is that pterostilbene works indirectly. It crosses the blood-brain barrier and somehow inhibits the mechanism that governs the synthesis of stress hormones known as glucocorticoids. Many cancers have a lot of glucocorticoid receptors; block those and the cancer cell's defenses decrease, making it more susceptible to treatments like chemotherapy.

"The good thing is that pterostilbene works," Estrela says. "The bad thing is that we cannot fully explain its potential health benefits with the information that we have."

Pterostilbene and Calorie Restriction

Calorie restriction has long been known as the best way to extend the lifespan of everything from yeast to mammals. Eating at least 30 percent fewer calories extends life by activating sirtuins, which are proteins that regulate cellular health. But the calorie restriction would be drastic, leading scientists to hunt for other ways to activate the seven known sirtuins in humans. Turns out, pterostilbene activates one called SIRT1, which plays a pivotal role in aging, including in DNA repair.

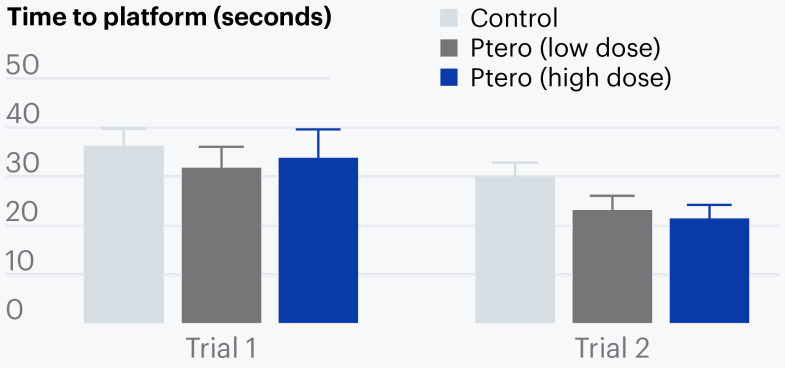
Sirtuins can only function with NAD+ (nicotinamide adenine dinucleotide), a coenzyme whose levels decrease as we age. A precursor to NAD+ is nicotinamide riboside (NR), a

vitamin found in trace amounts in milk. A 2012 study found that supplementing mice with NR increased levels of NAD+ — suggesting that NR might be good accompaniment to sirtuin-activating compounds like pterostilbene. And Elysium's 2017 double-blind, placebo-controlled human study found that NR supplementation through Basis increases NAD+ levels.

Pterostilbene Supplementation Improves Learning and Memory

Researchers placed aged rats in a Morris Water Maze, which times how long a rat takes to find a hidden platform in a bowl of water. Rats hate water, so they are incentivized to try and find it as quickly as possible.

The rats treated with high-dose pterostilbene found the hidden platform significantly faster during trial 2, showing that these rats had learned where the platform is.



Source: Joseph, James A., et al. "Cellular and Behavioral Effects of Stilbene Resveratrol Analogues: Implications for Reducing the Deleterious Effects of Aging." Journal of Agricultural and Food Chemistry, vol. 56, no. 22, 2008, pp. 10544–10551., doi:10.1021/jf802279h.

Pterostilbene for Health and Aging

Pterostilbene's connection to sirtuins is just one of the reasons longevity scientists are so excited by the compound. A 2008 study found that pterostilbene was effective in reversing cognitive decline in aging rats and that improved working memory — that is, short term memory — was linked to higher levels of pterostilbene in the hippocampus, the part of the brain that is involved in emotions, learning and memory formation. More recently, the compound was shown to be a potent modulator of cognition — with mice fed a pterostilbene-supplemented diet better able to make their way through a maze than the control group.

Researchers theorize that this is because the chemical activates a nuclear receptor protein called PPAR-alpha, which is involved in the regulation of cognition, anxiety, and emotional behavior.

"If you feed mice a pterostilbene-enriched diet they become more intelligent somehow," says Estrela. In this case, the definition of "more intelligent" is that they can find their food faster. They also learn and remember better.

Pterostilbene can also activate multiple signaling pathways in the human body that are protective, including one called NRF2, which is the master regulator of the cell's antioxidant response. When the body is under so-called oxidative stress — which is what damages cells — NRF2 goes and turns on all the enzymes needed to fight back. Among other things, oxidative stress damages DNA; accumulated DNA damage is part of the aging process.

Pterostilbene may also have wide-ranging applications for skin disorders — but first and foremost, it could be be a powerful protector against skin cancer in humans and animals. Applied topically, Pterostilbene isn't a sunscreen, like zinc, which actually shields the skin from UVA and UVB rays. Instead, pterostilbene acts indirectly by increasing the antioxidant defenses of the skin. Don't confuse "indirectly" with "sort of, kind of," by the way. Quite the opposite: In Estrela's lab, when mice were irradiated two times a week for six months, their entire backs were covered with carcinomas. But those who received the pterostilbene treatment had zero tumors.

Because pterostilbene also has anti-inflammatory effects, scientists have had success in mice models using it to treat psoriasis, atopic dermatitis, and contact/allergic dermatitis.

Pterostilbene could also help researchers studying colon cancer, the third-highest cause of cancer death – and one whose incidence is increasing among people younger than age 50. In human genes, the compound has been shown to inhibit growth in colon cancer cells (specifically more so than resveratrol).

In the liver, a 2005 study in mice found that pterostilbene (along with quercetin, a polyphenol found in apple skins and cherries) inhibited liver tumor growth up to 56 percent — and extended life, "the first time that in vivo administration of natural polyphenols shows inhibition of metastatic growth of a highly malignant tumor and extension of host survival." Scientists aren't sure why this works: One theory is that the polyphenols interfere with cell division. Cancer is unchecked cell division, but if something stops those cells from dividing, they die.

And more benefits of pterostilbene are likely to be uncovered. Consider this: There are about 11,000 published scientific papers about resveratrol, versus barely 400 on pterostilbene. But research on pterostilbene is at least 10 years behind resveratrol. Give it time.