Fruits and Vegetables Are Trying to Kill You

By *Moises Velasquez-Manoff* with comments by Vic Cherikoff*

Antioxidants from modern foods or synthetic vitamins don't stress us like plants do ... and they don't have their beneficial effects.

You probably try to exercise regularly and eat right. Perhaps you steer toward "superfoods," fruits, nuts, and vegetables advertised as "antioxidant," which combat the nasty effects of oxidation in our bodies. Maybe you take vitamins to protect against "free radicals," destructive molecules that arise normally as our cells burn fuel for energy, but which may damage DNA and contribute to cancer, dementia, and the gradual meltdown we call aging.

Warding off the diseases of aging is certainly a worthwhile pursuit. **But evidence has mounted to suggest that antioxidant vitamin supplements, long assumed to improve health, are ineffectual.** Fruits and vegetables are indeed healthful but not necessarily because they shield you from oxidative stress. In fact, they may improve health for quite the opposite reason: They stress you.

That stress comes courtesy of trace amounts of naturally occurring pesticides and anti-grazing compounds. You already know these substances as the hot flavors in spices, the mouth-puckering tannins in wines, or the stink of Brussels sprouts. They are the antibacterials, antifungals, and grazing deterrents of the plant world. In the right amount, these slightly noxious substances, which help plants survive, may leave you stronger.

Eating food from plants that have struggled to survive toughens us up as well.

Parallel studies, meanwhile, have undercut decades-old assumptions about the dangers of free radicals. Rather than killing us, these volatile molecules, in the right amount, may improve our health. Our quest to neutralize them with antioxidant supplements may be doing more harm than good.

The idea that pro-oxidant molecules are always destructive is "oversimplified to the point of probably being wrong," says Toren Finkel, chief of the Center for Molecular Medicine at the National Heart, Lung, and Blood Institute in Bethesda, Maryland. "**Oxidants may be a primordial messenger of stress in our cells, and a little bit of stress, it turns out, may be good for us**."

Although far from settled, a wave of compelling science offers a remarkably holistic picture of health as a by-product of interactions among people, plants, and the environment. Plants' own struggle for survival— against pathogens and grazers, heat and drought—is conveyed to us, benefitting our health. This new understanding begins, in part, on a treadmill.

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In the mid-20th century, as modern medicine seemed poised to vanquish the infectious diseases of yore, some scientists turned to the degenerative diseases associated with aging. Attention fell on a class of molecules called "reactive oxygen species," or ROS. These volatile substances could damage DNA. Degenerative diseases, such as cancer and cardiovascular disease, often showed evidence of "oxidative stress," suggesting that ROS spurred disease.

Oddly, our mitochondria, the energy factories of our cells, emitted ROS naturally. So **degenerative disease seemed to stem in part from our own metabolic function**: Your mitochondria "burned" fuel, emitted this toxic exhaust, and inadvertently set the limits on your existence. That was the working hypothesis, at any rate.

Experiments on rats and worms showed that reactive oxygen species, such as hydrogen peroxide, tear atoms from other molecules, destroying the remains in the process. That can be problematic when those molecules are DNA, our cellular instruction manual. We produce native antioxidants, such as the molecule glutathione, to counteract this pro-oxidant threat. They react with ROS, neutralizing the pro-oxidants before they can damage important cellular machinery.

When scientists blocked rodents' ability to manufacture these protective molecules, lifespan declined. Observational studies, meanwhile, suggested that people who regularly ate vitamin-laden fruits and vegetables were healthier. So were people with higher levels of vitamins E and C in their blood.

Vitamins were strongly antioxidant in test tubes. So the ROS theory of aging and disease rose to prominence. You could slow aging, it followed, by neutralizing free radicals with antioxidant pills. A supplement industry now worth $23 billion yearly in the U.S. took root.

But if those ROS were so harmful, some scientists asked—and the basic design of our (eukaryote) cells was over 1 billion years old—why hadn't evolution solved the ROS problem? At the same time**, scientists began finding that exercise and calorie restriction increased lifespan in animals. Both elevated ROS**. According to the ROS model of aging, animals that exercised and fasted should have died younger. But they lived longer.

For Michael Ristow, a researcher of energy and metabolism at the Swiss Federal Institute of Technology in Zurich, the inconsistencies became impossible to overlook. In worms, he found that neutralizing those allegedly toxic ROS reduced lifespan, so he designed a similar experiment in humans.

He had 39 male volunteers exercise regularly over several weeks; half took vitamin supplements before working out. The results, published in 2009, continue to reverberate throughout the field of exercise physiology, and beyond. Volunteers who took large doses of vitamins C and E before training failed to benefit from the workout. Their muscles didn't become stronger; insulin sensitivity, a measure of metabolic health, didn't improve; and increases in native antioxidants, such as glutathione, didn't occur.

Exercise accelerates the burning of fuel by your cells. If you peer into muscles after a jog, you'll see a relative excess of those supposedly dangerous ROS—exhaust spewed from our cellular furnaces, the mitochondria. If you examine the same muscle a short time after a run, however, you'll find those ROS gone. In their place you'll see an abundance of native antioxidants. That's because, post-exercise, the muscle cells respond to the oxidative stress by boosting production of native antioxidants. Those antioxidants, amped up to protect against the oxidant threat of yesterday's exercise, now also protect against other ambient oxidant dangers.

Contrary to the ROS dogma, Ristow realized, the signal of stress conveyed by the ROS during exercise was essential to this call-and-response between mitochondria and the cells that housed them. To improve health, he figured, perhaps we shouldn't neutralize ROS so much as increase them in a way that mimicked what happened in exercise. That would boost native antioxidants, improve insulin sensitivity, and increase overall resilience.

Ristow called this idea "mitohormesis." The term "hormesis" came from toxicology ("mito" was for mitochondrion). It describes the observation that some exposures generally considered toxic can, in minute amounts, paradoxically improve health. For instance, minuscule quantities of X-ray radiation, a known carcinogen, increases the lifespan of various insects.

Hormesis may be most easily grasped when considering exercise. Lift too much weight or run too long, and you'll likely tear muscle and damage tendons. But lift the right amount and run a few times a week, and your bones and muscles strengthen. The intermittent torque and strain increases bone mineralization and density. Stronger bones may better tolerate future shocks that might otherwise cause fractures.

In his experiment, Ristow saw that vitamin supplements interrupted this sequence of stress followed by fortification, probably because they neutralized the ROS signal before it could be "heard" elsewhere in the cell. **By interfering in the adaptive response, vitamins prevented the strengthening that would have otherwise followed the stress of physical exertion. Antioxidant supplementation paradoxically left you weaker**.

Vitamins are necessary for health. And supplements can help those who are deficient in vitamins. Insufficient vitamin C, for instance, causes scurvy, which results from defective collagen, a protein in connective tissue. Among other functions, vitamin C aids collagen synthesis.

But the primary role of vitamins in our body, according to Ristow and others, may not be antioxidant. And **the antioxidant content of (conventional) fruits and veggies does not, he thinks, explain their benefits to our health**. So what does?

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Mark Mattson, Chief of the Laboratory of Neurosciences at the National Institute on Aging, has studied how plant chemicals, or phytochemicals, affect our cells (in test tubes) for years. The assumption in the field has long been that, like vitamins, phytochemicals are directly antioxidant. But Mattson and others think they work indirectly. **Much like exercise, he's found, phytochemicals stress our bodies in a way that leaves us stronger**.

Plants, Mattson explains, live a stationary life. They cannot respond to pathogens, parasites, and grazers as we might—by moving. To manage the many threats posed by mobile life, as well as heat, drought, and other environmental stresses, they've evolved a remarkable number of defensive chemicals.

Health doesn't result solely from the instructions your genome contains, but your relationship with the world.

We're familiar with many components of their arsenal. The nicotine that we so prize in tobacco slows grazing insects. Beans contain lectins, which defend against insects. Garlic's umami-like flavor comes from allicin, a powerful antifungal (*although allicin is unstable and is only one of over 2000 biologically active compounds in the 300 known cultivars of garlic - VC note*). These "antifeedants" have evolved in part to dissuade would-be grazers, like us.

Mattson and his colleagues say these plant "biopesticides" work on us like hormetic stressors. Our bodies recognize them as slightly toxic, and we respond with an ancient detoxification process aimed at breaking them down and flushing them out.

Consider fresh broccoli sprouts. Like other cruciferous vegetables, they contain an antifeedant called sulforaphane. Because sulforaphane is a mild oxidant, we should, according to old ideas about the dangers of oxidants, avoid its consumption. Yet studies have shown that eating vegetables with sulforaphane reduces oxidative stress.

(Note from VC) But to get the benefits from sulphoraphane, we need to have the plant make it. We know that sulphoraphane is the product of an extra-cellular reaction between and enzyme (myrosinase) and a carbohydrate substrate (glucoraphanin and other glucosinolates). To have this happen, we need to follow a recipe: Firstly, choose your Brassica oleracea cultivar which might be one or several from this list; broccoli, broccolini, Brussels sprouts, kale, cauliflower, cabbage, kohlrabi, collard greens, savoy cabbage. Daikon radish is also a contender. Next, stir-fry the coarsely-chopped vegetable trying to keep the temperature at 60°C. Remove from heat and blend to a purée. Leave the mash at room temperature for up to 90 minutes before consuming it. There is a lot of biochemistry in these steps and temperature and time are all important..

When sulforaphane enters your blood stream, it triggers release in your cells of a protein called Nrf2. This protein, called by some the "master regulator" of aging, then activates over 200 genes. They include genes that produce antioxidants, enzymes to metabolize toxins, proteins to flush out heavy metals, and factors that enhance tumor suppression, among other important health-promoting functions.

In theory, after encountering this humble antifeedant in your dinner, your body ends up better prepared for encounters with toxins, pro-oxidants from both outside and within your body, immune insults, and other challenges that might otherwise cause harm. By "massaging" your genome just so, sulforaphane may increase your resistance to disease.

In a study on Type 2 diabetics, broccoli-sprout powder lowered triglyceride levels. High triglycerides, a lipid, are associated with an increased risk of heart disease and stroke. Lowering abnormally elevated triglycerides may lessen the risk of these disorders. In another intervention, consuming broccoli sprout powder reduced oxidative stress in volunteers' upper airways, likely by increasing production of native antioxidants. In theory, that might ameliorate asthmatics' symptoms.

Elevated free radicals and oxidative stress are routinely observed in diseases like cancer and dementia. And in these instances, they probably contribute to degeneration. But they may not be the root cause of disease. According to Mattson, **the primary dysfunction may have**

occurred earlier with, say, a creeping inability to produce native antioxidants when needed, and a lack of cellular conditioning generally.

Mattson calls this **the "couch potato" problem**. Absent regular hormetic stresses, including exercise and stimulation by plant antifeedants, "cells become complacent," he says. "Their **intrinsic defenses are down-regulated**." Metabolism works less efficiently. Insulin resistance sets in. We become less able to manage pro-oxidant threats. Nothing works as well as it could. And this mounting dysfunction increases the risk for a degenerative disease.

Implicit in the research is a new indictment of the Western diet. Not only do highly refined foods present tremendous caloric excess (*and our molly-coddled produce lacks stress-induced pro-oxidants*), they lack these salutary signals from the plant world—"signals that challenge," Mattson says. Those signals might otherwise condition our cells in a way that prevents disease.

Another variant of the hormetic idea holds that our ability to receive signals from plants isn't reactive and defensive but, in fact, proactive. We're not protecting ourselves from biopesticides so much as sensing plants' stress levels in our food.

Harvard scientist David Sinclair and his colleague Konrad Howitz call this xenohormesis: benefitting from the stress of others. Many phytonutrients trigger the same few cellular responses linked to longevity in eukaryotic organisms, from yeasts to humans. **Years of research on Nrf2 in rodents suggest that activating this protein increases expression of hundreds of health-promoting genes, including those involved in detoxification, antioxidant production, control of inflammation, and tumor suppression.**

In the dance between animals and plants, there's true mutualism. "We're in this together, the plants and us."

Sinclair studies another class of native proteins, called sirtuins, associated with health. They're triggered by exercise and also, Sinclair contends, a molecule called resveratrol, found in grape skins and other plants. "It's too coincidental that time and time again these molecules come out of nature that have the surprising multifactorial benefit of tweaking the body just the right way," Sinclair says.

They're not all antifeedants, he argues. Plants churn these substances out when stressed, prompting further adaptations to the particular threat, be it drought, infestation by grazing insects, or excessive ultraviolet radiation from the sun.

For grazers, these stress compounds in plants may convey important information about environmental conditions. So grazers' ability to "perceive" these signals, Sinclair argues, likely proved advantageous over evolutionary time. It allowed them to prepare for adversity. A grape vine stressed by fungi churns out resveratrol to fight off the infection. You drink wine made from those grapes, "sense" the harsh environmental conditions in the elevated tannins and other stress compounds, gird your own defenses, and, in theory, become more resistant to degenerative disease.

One implication is that modern agriculture, which often prevents plant stress with pesticides and ample watering, produces fruits and vegetables with weak xenohormetic signals. "I buy stressed plants," Sinclair says. "Organic is a good start. I choose plants with lots of color because they are producing these molecules." Some argue that xenohormesis may explain, at least in part, why the Mediterranean diet is apparently so healthful. It contains plants such as olives, olive oil, and various nuts that come from hot, dry, stressful environments. ***Additionally, we should also recognize that the traditional Mediterranean diet was based on hundreds of local wild foods (note from VC)***. Eating food from plants that have struggled to survive toughens us up as well.

Philip Hooper, an endocrinologist at the University of Colorado Anschutz Medical Campus, points out that plant-animal relationships are often symbiotic, and communication goes both ways. One example of direct plant-to-animal, biochemical manipulation comes from the coffee bush. Flowering plants compete with one another for the attention of pollinators, such as bees. Coffee bushes seem to gain advantage in this "marketplace" by using caffeine. The drug excites pollinators' neurons, etching the memory of the plant's location more deeply in their brains. Some think that biochemical tweaking increases the probability that the pollinator, which faces a panoply of flower choices, will return to that particular coffee bush.

In the dance between animals and plants, says Hooper, "I think there's true mutualism. We're in this together, the plants and us."

While xenohormesis is a compelling idea, it remains unproven. Barry Halliwell, a biochemist at the National University of Singapore, and an expert on antioxidants, has seen the dietary fads, from vitamins to fiber, come and go. He says the hormetic and xenohormetic ideas are plausible, but not certain. Various studies suggest that people who consume a lot of fruits and vegetables have healthier lifestyles generally. Those people probably go easy on the junk food, which alone may improve health.

Even within the hormetic idea, Halliwell sees the attempts to bore down on the individual chemicals as problematic. "That's worked very well in pharmacology, but it hasn't worked at all well in nutrition," he says. He doesn't think any single phytonutrient will explain the apparent health-promoting benefits of fruits and veggies. "Variety seems to be good," he says. That critique speaks to a larger problem: It's often unclear how lab research on simple organisms or cell cultures will translate, if at all, into recommendations or therapies for genetically complex, free-living humans.

What works in genetically uniform organisms, or cells, living in highly controlled environments, does not necessarily work in people. Human studies on resveratrol in particular have yielded contradictory results. Proper dosage may be one problem, and interaction between the isolates used and particular gene variants in test subjects another. **Interventions usually test one molecule, but fresh fruits and vegetables present numerous compounds at once. We may benefit most from these simultaneous exposures.**

The science on the intestinal microbiota promises to further complicate the picture; our native microbes ferment phytonutrients, perhaps supplying some of the benefit of their consumption. All of which highlights the truism that Nature is hard to get in a pill.

These caveats aside, research into xenohormesis reminds us that we are not at the complete mercy of our genetic inheritance. Genes matter, but health depends in large part on having the right genes expressed at the right time—and in the right amount. If our genome is a piano, and our genes are the keys, health is the song we play on the piano. The science on hormesis, the stresses that may keep us strong, provides hints about what kind of song we should play. Keep the body conditioned with regular exercise. Keep your cells' stress-response pathways intermittently engaged with minimally processed, plant-based food.

These recommendations end up sounding rather grandmotherly—if your grandmother was a spartan, no-nonsense peasant who lived off the land. But the underlying thrust contradicts assumptions about the need to protect oneself from hardship. Certain kinds of difficulty, it turns out, may be required for health. That's because **health doesn't result solely from the instructions your genome contains, but from your relationship with the wider world**. **Resilience isn't completely inherent to your body; it's cultivated by outside stimuli. And some of those stimuli just happen to be mildly noxious, slightly stressful chemicals in plants.**

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