The Genius of Nrf2

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Sixty years ago cardiologist and chemist Denham Harman published a revolutionary paper that changed the way we viewed health and longevity. Harman suggested an idea that is now second nature to us all—he proposed aging is due in part to the damage caused by “free radicals,” molecules that have a single unpaired electron in an outer shell, rendering them highly reactive and damaging. Free radicals are generated by cellular metabolism, as well as by toxicants from the environment.

The energy of life is like a fire, and fire must be controlled or it eventually it will consume the forest. Harman’s theory got a huge boost in 1969, when a University of Alabama graduate student named Joe McCord, and his mentor, Irwin Fridovich, published monumental findings on the potency and necessity of the endogenous antioxidant, superoxide dismutase (SOD), which helps quench the important free radical, superoxide. In fact, later research has shown that catalase, another potent antioxidant enzyme, present in all aerobic cells, can turn 6 million molecules of hydrogen peroxide to oxygen and water every single minute. Now that’s one potent antioxidant!

Harman was never able to actually extend the maximum lifespan—the age at which the oldest known member of a species has died. He thought about why that was so, and in 1972 published another remarkable paper suggesting that mitochondria, the energy powerhouses inside our cells, produce and are damaged by free radicals when they create energy. It is understood that it is very hard to migrate antioxidants through our own cell membranes and then through the double-membrane of the mitochondria. Harman concluded that mitochondrial integrity and function determine our maximum lifespan.

He was likely right on all counts. Science now understands that aging, and the degenerative diseases associated with aging, are in part due to our slowly declining ability to defend ourselves against free radical damage. These free radicals include superoxide, hydrogen peroxide, and peroxynitrite. Although these molecules have the ability to help kill invading microorganisms, they also have potential for damaging our cells and their lipid membranes. We now understand that through a healthy diet and exercise, as well as judicious supplementation with antioxidant nutrients, we may slow that process and help our bodies repair that inevitable damage.

Antioxidants familiar to us all include Vitamins E and C, glutathione, lipoic acid, melatonin, carotenoids, and natural flavonoids.

Nrf2: Master Antioxidant Switch

The free radical theory offered us a new lens by which to understand aging and degenerative illness. But one huge question has always remained: how does a cell manage to sense oxidative damage and then generate or utilize antioxidants to repair itself? Today, we are beginning to unravel the answer, and it centers on a potent master regulator of cellular repair, an intracellular transcription factor called Nuclear factor erythroid-derived 2-like 2 (Nrf2). Evolution generated a masterpiece when it crafted Nrf2. Nrf2
is the name for a cellular switch that orchestrates antioxidant, detoxification, and cellular defenses. When activated, Nrf2 can switch on over 200 genes that help the cell generate its own highly protective molecules. These molecules are crucial in the metabolism of drugs and toxins. They protect against oxidative stress and inflammation, remove damaged proteins, and initiate DNA repair. In fact, the Nrf2 pathway is emerging as an astonishingly rich area of research in immunological, neurological disorders, and in cancer research. Currently, there are over 1,000 peer reviewed studies published a year on this pathway alone.

Nrf2 is widely distributed in all mammals. It is the result of a billion years of evolution, and is highly complex and highly conserved as a system. The diversity of Nrf2’s many target genes shows its vital importance in cell survival and in life itself and is expressed in all tissues, although the key detoxification organs (the kidney and liver) exhibit the highest levels.

Nrf2 provides us unexpected insight into the dance of life itself—the dance of fire and water—of oxidants and antioxidants. Our Nrf2 system is self-healing. It has evolved to protect us against the slings and arrows of life, and it is consequentially stimulated into action by these and other stressors. Many health-enhancing molecules that we have long thought of as potent antioxidants, work in part by upregulating Nrf2. Even some of our most potent cancer-fighters work because they activate our own substantive cell-protective defenses. These molecules offer protection that goes far beyond their known roles as antioxidants and singlet oxygen scavengers. They may help explain how health and longevity diets may work (because they are rich in Nrf2 stimulators). By acting as ‘low-dose stressors,’ these constituents of healthy diets may actually prepare us to resist more severe stress. Nrf2 is likely one reason that sulforaphane in broccoli is a potent cancer and inflammation fighter—sulforaphane is now known to successfully activate Nrf2.

Nrf2 teaches us that life, and our body, is in a dynamic balance. Some scientists think that Nrf2 is the master regulator of the aging process itself, and that the protective role of Nrf2 against toxins and the growth of tumors actively determines longevity and healthspan. Raising Nrf2 activity is likely to be of particular importance to the hundreds of millions of people around the globe who are regularly exposed to toxic chemicals that contribute to diseases characterized by oxidative stress, inflammation and mitochondrial dysfunction, diseases which include many of the chronic diseases of 21st century life.

How Does Nrf2 Work? A Quick Guide

Nrf2 first emerged from obscurity in 1997, when a biochemist named Masayuki Yamamoto at the University of Tsukuba in Japan showed that it activates an entire class of detoxifying enzymes.

Nrf2 usually hums along in the cell at low levels and is activated only when a cell is under stress. Until that moment, it is kept quietly in check by a molecule known as Keap1. When a cell is suitably stressed (including by pro-oxidants), Keap1 is stimulated to let go of its hold on Nrf2, which then moves into the nucleus of the cell and triggers a wide range of genes called antioxidant response element (ARE)-bearing genes. These ARE-bearing genes churn out powerful natural antioxidants and Phase II liver detoxifying enzymes, which safely denature and quench electrophiles, reactive oxygen and nitrogen species, and help the cell remove damaged proteins, quench inflammation, and repair itself.

As soon as the trigger passes, Keap1 escorts Nrf2 out of the nucleus and it is broken down. Nrf2 then returns to its normal, low-level resting state, and the cell’s molecular switch is set to “off” until the next stressor comes along. The Keap1-Nrf2 bond is an ingenious invention of evolution, creating a
molecular switch that is exquisitely sensitive to environmental and molecular triggers.

Nrf2 turns out to be a key modulator of glutathione. Reduced glutathione (GSH) has often been described as the most important low molecular weight antioxidant produced in the human body. Each of the three genes that encode enzymes required for the synthesis of GSH are activated by Nrf2, as is the gene for glutathione reductase, the enzyme that converts oxidized glutathione (GSSG) to GSH. But Nrf2 doesn’t stop there. The most potent antioxidant enzymes in our body include superoxide dismutase and catalase. Two superoxide dismutase genes (SOD1 and SOD2) are activated by Nrf2, with each SOD lowering oxidative stress by lowering superoxide. Catalase and two glutathione peroxidase genes are each induced by Nrf2, with each of these enzymes acting to lower hydrogen peroxide produced from superoxide.

To the hundreds of millions of people around the world exposed daily to substantial levels of toxicants, detoxification may be Nrf2’s most remarkable gift to us. Numerous Nrf2 genes contribute to detoxification of xenobiotics (toxic chemical compounds) and heavy metals. Upregulation of Nrf2 also has astounding anti-inflammatory effects including lowering many inflammatory mediators such as cytokines, chemokines, and adhesion molecules. Nrf2 also helps spur the formation of new mitochondria—the energy and immune system powerhouses that stud our cells and regulate cellular respiration and metabolism. This is called mitochondrial biogenesis, and it is impaired as we age. Nrf2 activation increases the efficient use of fuel (fatty acids and glucose) by mitochondria and increases energy production. It also promotes muscle repair and recovery and reduces muscle injury.

The traditional Mediterranean diet and the traditional Okinawan diet are both heavy in Nrf2 stimulators. They are thought to be two of the most healthful human diets known to humans, and include some of the longest living and healthiest older adults.

In sum, Nrf2 responds to a wide range of cellular stresses. This includes toxicants of all kinds, some pro-oxidants, exercise, and the many health-promoting phytochemicals in fruits and vegetables. At first glance, this seems counterintuitive. Why would our most healing foods, our richest source of vitamins, minerals and antioxidants, also contain mild toxicants that initiate our cell’s master healing switch?

On further thought, this makes sense. These molecules are messengers to us about our environment. How does any fruit, vegetable, or plant survive and thrive while being attacked by pathogens, predators and weather extremes? One way is by churning out a wide range of powerful molecules to protect itself—not just self-repairing molecules but bitters, tannins, toxicants and oxidants to defend against harsh conditions. Fruits and vegetables are not only power-packed with nutrition; they contain a chemical map of their own immunological survival mechanisms, and the ability to trigger our own Nrf2. They are messengers and allies. A grape vine stressed by too much sun, too many predators or pathogens, churns out resveratrol and protective tannins. We eat the grapes and our body responds to the phytochemicals by elevating Nrf2, protecting us and theoretically increasing our own resistance to disease and stress. Is it any wonder that a diet generous in nutrient rich, Nrf2-stimulating fruits and vegetables slashes rates of cancer and all-cause mortality?

In fact, the traditional Mediterranean diet and the traditional Okinawan diet are both heavy in Nrf2 stimulators. They are thought to be two of the most healthful human diets known to humans, associated with high overall lifespans, large numbers of centenarians and low incidences of cancer and cardiovascular disease. The traditional Mediterranean diet relies heavily on olives and olive oil, which contain very high levels of Nrf2 stimulating phenols and...
terpenes. The purple sweet potato is the staple of the traditional Okinawan diet and is very high in carotenoids and anthocyanins, which are potent Nrf2 activators. Nrf2 likely has a major role in the health promotion in each of these two diets.27,28,29

**It’s No Surprise: Nrf2 Research is Exploding**

In recent years, researchers of every ilk have begun to explore the power of Nrf2. Some are elucidating its basic mechanisms. Some are exploring its ability to oscillate at different speeds, or defining its true molecular weight.30

But perhaps most exciting is the research into Nrf2 and many devastating human illnesses: Multiple Sclerosis, Parkinson’s, Huntington’s, cancer, and diabetes. These diseases each appear separate—with distinct causes and symptom pictures—and yet all involve oxidative stress. No wonder a wealth of Nrf2 research is focusing on so many of them, with fascinating new findings suggesting that Nrf2 can eventually be tweaked to possibly relieve and slow many terrible illnesses—and maybe even slow aging.

**Multiple Sclerosis:** Multiple sclerosis (MS) affects 2.1 million people around the world, and there is currently no treatment that will cure the disease, though medications can help slow its progression and ease symptoms. A newly approved oral medication for MS, Dimethyl fumarate (DMF), activates the Nrf2 pathway and lowers oxidative stress. It significantly reduces relapses and brain lesions. DMF increases the concentration of Nrf2 in the cell, and promotes the activity of ARE-genes downstream of Nrf2. Extensive and rigorous clinical trials have assessed the efficacy and safety of DMF.31,32

**Parkinson’s Disease:** Nrf2 research has received grants from The Michael J. Fox Foundation. Numerous studies suggest that activation of the Nrf2–ARE pathway in the brain offers protection to vulnerable neurons, making neuronal Nrf2 up-regulation an attractive therapeutic strategy for Parkinson’s Disease (PD). Research is focusing on novel compounds that cross the blood–brain barrier and activate the Nrf2-ARE pathway in the brain. The hope is such compounds could halt the progression of PD.33

**Diabetes:** As it progresses, diabetes impairs antioxidant capacity in the heart, including Nrf2. The American Diabetes Foundation is sponsoring a study on Nrf2 and cardiac health. Researchers at the University of Louisville in Kentucky are looking at both Type 1 and Type 2 diabetes. Research has already shown that Nrf2 protects the heart from high levels of glucose. Nrf2 is down regulated in diabetic patients. Studies in mice show that a novel Nrf2 activator, known as dh404, protects the animals from heart damage due to diabetes. If Nrf2 can help prevent diabetes-related heart problems, the researchers plan to develop dietary supplements that upregulate cardiovascular levels of Nrf2.34

**Epilepsy:** In 2013, Epilepsy Research UK awarded Matthew Walker and colleagues at University College London a grant to study Nrf2 pathways in seizure induced cell death by two pathways.35,36

**Huntington’s Disease:**

The rapidity with which damaged proteins are cleared from neurons may affect cell survival and may explain why some cells die in neurodegenerative disorders. To test this idea, researchers activated Nrf2, which allowed neurons to live longer.37 The scientists used optical pulse-labeling, a new technology that allowed them to actually monitor individual neurons in real time.

In Huntington’s disease and many other neurodegenerative disorders, proteins that are misfolded (have abnormal shapes), accumulate inside and around neurons and are thought to damage and kill nearby brain cells. Normally, cells sense the presence of malformed proteins and clear them away before they do any damage. This study was supported by a grant from the National Institute of Neurological Disorders and

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**As we gain a richer understanding of Nrf2, we can focus on exciting new ways of raising Nrf2, when appropriate, and substantially lowering many health risks of modern life.**
In Focus
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Stroke (NINDS). “Nrf2 seems like a potentially exciting therapeutic target. It is profoundly neuroprotective in our Huntington’s model and it accelerates the clearance of mutant huntingtin [a gene potentially important for long-term memory storage],” said principal investigator Steven Finkbeiner.

Cardiovascular Disease: Nrf2 also suppresses multiple proinflammatory genes, including tumor necrosis factor α (TNF-α), and the interleukins (IL-1b, IL-6) as well as prostaglandins, matrix-metalloproteinases, and nitric oxide synthase.\(^{38}\) Downregulating inflammation benefits the entire cardiovascular system. Nrf2 has been shown to protect arterial endothelial cells from inflammation.\(^{39,40}\) The Nrf2 pathway is crucial in protecting the cardiovascular system against oxidative damage by reactive oxygen species.\(^{41}\)

Longevity: “The strong relationship between species longevity and cellular resistance to oxidative insults has been reported in a wide variety of organisms across the animal kingdom,” write researchers at the University of Texas at San Antonio. Mice who have no Nrf2 at all look normal, but are more susceptible than their Nrf2 carrying peers to hyperoxia, lipopolysaccharide (LPS), cigarette smoke, diesel exhaust fumes, ultraviolet irradiation (UVA and UVB), as well as toxic chemicals.\(^{42}\)

Top Nrf2 Nutrients Available Now
In spite of the flurry of research on Nrf2, safe pharmaceuticals that increase its activity are a long way off. Yet diet, lifestyle and targeted nutrients can gently and safely support healthy Nrf2 management now. Many polyphenols in plants stimulate Nrf2, as do to-

SuperBerry Yogurt Sorbet

This delicious, refreshing sorbet is naturally sweet with an array of berries. It was created by Christine Bailey, MSc, PGCE, MBANT, CNHC, for raising Nrf2 in a nourishing and healthy dessert that is rich in probiotics and fiber. The combination of ProBerry Amla powder, which is packed with Nrf2 stimulating berries, along with regular fresh or frozen berries, makes for a delicious treat. Christine is Director of Advance Nutrition in the UK, television chef and health consultant. Her website is www.christinebailey.co.uk.

Ingredients:

- 200ml/7fl oz/scant 1 cup natural yogurt, soya yogurt or coconut yogurt
- 1 scoop of ProBerry Amla Powder
- 125g/4½ oz/heaped ¾ cup strawberries
- 125g/4½ oz/1 cup raspberries
- 225g/8 oz/heaped 1 cup fresh or frozen cherries, pitted


Directions:

1. Put all the ingredients into a high speed blender and process until smooth and creamy.
2. Pour into an ice cream maker and churn according to the manufacturers instructions. Alternatively pour into a shallow freezer-proof container and freeze for 2–3 hours or until firm.
3. Remove from the freezer 30 minutes before serving to allow it to soften slightly. (Store in the freezer for up to 3 months.)

Serves 4
Preparation time: 5 minutes, plus freezing time

Nutritional information per serving
Protein 4g, Carbohydrate 12.2g of which sugars 11.5g, Fat 5.3g of which saturates 3.4g, Kcals 110
copherols and tocotrienols, sulfur compounds from the garlic and onion family, carotenoids, fish oil, and molecules such as Ginkgo biloba, pomegranate extract, and silymarin, among others. Here is a list of some potent, dietary Nrf2 inducers with substantial peer review research already available. These nutrients are easily found in fruits, vegetables, and as dietary supplements.

**Sulforaphane:** Sulforaphane is a phytochemical found in cruciferous vegetables such as broccoli, cabbage, kale, collard greens, cauliflower, bok choy, and Brussels sprouts. It is especially concentrated in broccoli sprouts. Sulforaphane is a hotbed of research: over 1200 peer-reviewed studies have been published on this one phytochemical since 1992.

Sulforaphane is one of the most potent natural inducers of Nrf2, acting first on Keap1. It is able to accumulate in cells and actually swap function with glutathione, effectively handling oxidation. Its protective role in cancer is particularly profound. Recent studies on sulforaphane and Nrf2 span the gamut, demonstrating its ability to protect the retina, kidney, lung, liver and skin specifically by activating Nrf2.

Sulforaphane from broccoli sprouts has been studied as possible liver cancer prevention in China where rates of this cancer are particularly high. Residents of Qidong often suffer from chronic infection with hepatitis B virus, and are exposed to high levels of aflatoxins in mold-contaminated produce. As a result, hepatocellular cancer is responsible for up to 10% of the adult deaths in areas.

Clinical trials in the Qidong province of China found that broccoli sprouts increase excretion of many toxins, from mold toxins to pollutants. Freeze-dried standardized sprout extracts from select cultivars were utilized in multiple studies, and hot water extracts in others. A team from Johns Hopkins University School of Medicine and Bloomberg School of Public Health, in collaboration with scientists at the Qidong Liver Cancer Institute in Shanghai gave a hundred individuals five ounces of broccoli sprouts extract, and another hundred individuals drank a placebo. Tests of subjects’ urine showed carcinogens were being excreted from the body in those who drank the active extract. Statistically significant increases of 20-50% in the levels of excretion of chemicals from airborne pollutants (acrolein, crotonaldehyde and benzene) were seen in individuals receiving sulforaphane from broccoli sprouts.

The researchers conclude that, “Prevention trials of whole foods or simple extracts offer prospects for reducing an expanding global burden of cancer effectively with minimal cost.” In another study, Researchers found a significant association between excretion of total sulforaphane metabolites and excretion of aflatoxin.

**Resveratrol:** Resveratrol is a potent antioxidant found in more than 70 species of plants, including grapes, cranberries, blueberries, mulberries, lingonberries, bilberries, jackfruit, peanuts, chocolate, as well as Asian plant roots. It is a plant-derived polyphenol that is beneficial for the neurological, hepatic, and cardiovascular systems and seems to slow down aging, mimicking the effects of caloric restriction. It is reported to extend longevity in yeast, nematodes (worms) and flies.

For at least ten years now, resveratrol has stimulated wide-ranging research into its potential therapeutic benefits. In fact, resveratrol is thought to be the red wine molecule that explains the famous “French paradox” (the French, who consume a lot of red wine, have less coronary heart disease than expected, given their high fat diets). And yet until we began to unravel its role in upregulating Nrf2, the actual molecular and cellular mechanisms of this potent antioxidant were elusive. Resveratrol, it appears, is a strong trigger of Nrf2, enhancing function of the endocrine, cardiovascular, and nervous systems.

According to a 2010 review article by researchers at NIH and New Jersey Medical School, resveratrol may offer a safe way to target several pathways involved in the development of cardiovascular diseases. Resveratrol has been shown to help attenuate insulin resistance, and may be a useful strategy for protecting against diabetes. It may help prevent breast cancer; in animal studies, supple-
mentation with resveratrol alone or in combination with the protective form of estrogen significantly upregulated expression of Nrf2 in mammary tissue. Resveratrol also prevented estrogen-mediated inhibition of detoxification genes. Resveratrol treatment induced death of malignant cells and inhibited an estrogen-mediated increase in DNA damage in mammary tissues. Taken together, these results suggest that resveratrol inhibits estrogen-linked breast cancer via Nrf2-mediated protective pathways.55

Resveratrol may help protect against lung cancer associated with cigarette smoking. Cigarette smoke depletes glutathione (GSH) levels in the lung’s alveolar epithelial cells. Resveratrol restored glutathione levels in human alveolar epithelial cells in part through the Nrf2 pathway. The researchers conclude that “these data may have implications in dietary modulation of antioxidants in treatment of chronic obstructive pulmonary disease.”56 There are many other powerful studies suggesting that resveratrol’s benefits are linked to Nrf2.

Silymarin: Silymarin, from the plant milk thistle, is a unique blend of three flavonoids, silybin, silydianin, and silychristin. Silymarin is well known as a potent antioxidant that has profound protective effects on the liver. It has been demonstrated to help generate new liver cells damaged by alcohol or drugs, stimulate bile flow and reduce liver/gall-bladder stagnation, increase the survival rate of patients suffering from cirrhosis, and protect the liver against all kinds of poisons and pharmaceuticals and protect the kidneys in diabetic nephropathy.57,58,59,60 In healthy individuals, silymarin raises glutathione in the liver by more than a third.61 Silymarin also increases the level of the important antioxidant enzyme superoxide dismutase in cell cultures.62

Silymarin also appears to protect against cancer, including prostate cancer.63 It also shows potentially protective effects in an astounding range of other cancers: colon, ovarian, skin, lung, breast and cervical cancers.64,65,66 But silymarin appears to offer protection far beyond the liver and potentially cancer. New research suggests that it may benefit the kidneys, protect the heart, guard against insulin resistance, and even help prevent Alzheimer’s disease.67

How can one phytochemical from one single plant pack all this protective power? One way is via Nrf2 activation. Silymarin increases the movement of Nrf2 into the nucleus.68

Oleuropein: The olive tree is highly resistant to disease, in large part due to a bitter compound in both raw olives and olive leaf called oleuropein. It has been shown to lower blood pressure, increase blood flow in the arteries,
and inhibit the growth of pathogens through bactericidal, antiviral and antifungal activity. It is antioxidant, antiatherogenic, anti-cancer, anti-inflammatory and has antimicrobial properties.\textsuperscript{69,70,71} It is neuroprotective as well.\textsuperscript{72}

It is not surprising that oleuropein appears to upregulate Nrf2. In new research, both oleacine (a polyphenol in olive oil) and oleuropein were restorative via increasing heme oxygenase-1 (HO-1) by upregulating Nrf2.\textsuperscript{73} Synthetic analogues of oleuropein are impressively potent, and also work by upregulating Nrf2.\textsuperscript{74}

**Ginkgo biloba, Pomegranate, and Green Tea Polyphenol**

Many other nutraceuticals stimulate Nrf2 activity. Here are just a few:

**Ginkgo biloba** is one of the longest living tree species in the world. Trees of this species can live a thousand years. *Ginkgo biloba* is well known as a powerful antioxidant with a special affinity for vascular tissue.\textsuperscript{75} Folklore uses include stroke, memory problems, erectile dysfunction, vision problems, and asthma. It may also protect against radiation damage. New research shows its protective ability may be mediated by Nrf2, which under the influence of Ginkgo helps stimulate Phase II detoxifying enzymes in the liver. A recent study found that Nrf2 content in the nucleus of the cell was raised by *Ginkgo biloba* extract. Ginkgo appears to act on Keap1, inhibiting its reten-

tion related activity so that more Nrf2 is released.\textsuperscript{76}

Another study suggests that *Ginkgo biloba*’s ability to activate Nrf2 is responsible for its vascular protective effects, which triggers the increased activity of a gene called Heme-oxygenase-1.\textsuperscript{77} Heme oxygenase is an enzyme that degrades heme. Heme is the deep red, oxygen-carrying, nonprotein, iron component of hemoglobin. Heme oxygenase is induced by oxidative stress, and in animal studies it has been shown that increasing this expression seems to be protective.\textsuperscript{78}

**Pomegranate** is an ancient fruit, well known for its antioxidant features. Pomegranate possesses remarkable antioxidant properties capable of protecting normal cells from oxidative stress and cell death. The fruit contains at least three powerful anthocyanidins (delphinidin, cyanidin, and pelargonidin), which quench free radicals.\textsuperscript{79}

New research points pomegranate in the direction of Nrf2. A 2011 animal study, for instance, shows that pomegranate extract reduced the incidence, number, size and volume of liver nodules, which are a precursor to liver cancer. The study also found that pomegranate extract increased Nrf2 expression.** Green tea** contains a potent polyphenol, Epigallocatechin-3-gallate (EGCG), which has proven neuroprotective effects in animal studies. EGCG protects mouse neurons in Parkinson’s disease, and in mouse models of ALS.\textsuperscript{82} Other mice studies found that EGCG inhibits amyloid plaque formation and reduces cognitive impairment.\textsuperscript{83} EGCG increases distribution of Nrf2 in the nucleus of the cell, and modestly upregulates numerous Nrf2 target genes.\textsuperscript{84} EGCG may also help prevent cancer; tea polyphenols have been extensively studied in cell culture and animal models where they inhibited tumor onset and progression.\textsuperscript{85} Green tea consumption is linked to heart health, and appears in part to be due to Nrf2, activating heme oxygenase-1 (HO-1). At the molecular level, EGCG treatment significantly activates Nrf2 activity.\textsuperscript{86}

**New Insights Yield New Approaches**

Every health conscious individual recognizes that organic produce is generally healthier than conventional produce. Organic produce offers higher levels of vitamins and minerals, and lower levels of toxic metals and pesticides, according to the most comprehensive scien-
tific analysis to date. The role of a gene amplifier and cellular detoxifier has been extensively explored, and further comprehension is added every few weeks. But one simple observation we can draw from all of the remarkable new science is that antioxidant mechanisms are among the most important in the evolution of life on earth. Nrf2 produces complex and well-coordinated detoxification, immunity, anti-inflammatory, mitogenesis and other healthful effects. As we gain a richer understanding of Nrf2, we can focus on exciting new ways of raising Nrf2 and substantially lowering many health risks of modern life, with our constant exposure to xenobiotic toxins, pollutants, toxic metals and other adverse sources of oxidative stress.

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II detoxification. That’s how I got interested. Studying Nrf2 allows me to combine my interest in exploring mechanistic regulation of cellular signaling pathways with my training in toxicology.

**In Focus:** In the years since that time, interest in Nrf2 has exploded. There are over a thousand studies published annually. Can you explain, in the simplest of terms, why this pathway is so important, and how it gets activated or quieted down?

**DZ:** In one sense, the Nrf2 pathway is our very life. It is critical for maintaining cellular redox homeostasis, and it activates a whole range of genes that protect the cell by signaling our body to produce antioxidants and detoxifying enzymes. Nrf2 can protect cells and tissues from a variety of toxicants and carcinogens by increasing the expression of innumerable genes. As a result, several Nrf2 activators are currently being tested as chemopreventive and protective compounds in clinical trials. This is a very promising strategy for cancer prevention.

*Nrf2 is activated by many dietary ingredients, and you can eat certain foods or take dietary supplements to help enhance the pathway. One example is sulforaphane, a molecule with anti-cancer activity, found in broccoli and broccoli sprouts. This molecule has been demonstrated to protect against liver cancer in over fifteen years of clinical trials in China. Scientists have shown that broccoli sprouts made into a tea are effective in helping lower the risk of liver cancer. The sprouts do this by activating Nrf2. That’s just one of many examples of dietary influence. We are now working on a potent and nontoxic molecule derived from carrots, which upregulates Nrf2 and is showing great promise in preliminary research.*

**In Focus:** How do these dietary compounds upregulate Nrf2 activity?

**DZ:** Nrf2 is normally regulated by a molecule called Keap1. Keap1 keeps Nrf2 at low levels by targeting Nrf2 degradation in your body most of the time. You only need Nrf2 when your body encounters stress in the form of toxicants, carcinogens, even exercise. At that point Keap1 loosens its hold on Nrf2 and in a sense sets it free from destruction. When you eat something like broccoli sprouts, they inactivate Keap1, allowing Nrf2 to increase temporarily. The upregulation of Nrf2 is, by nature, intermittent, and tightly regulated.

**In Focus:** In some of your papers, you’ve highlighted the double edged sword of Nrf2. It can protect the cell from all kinds of insults—but that the pathway can also be hijacked by cancer cells for their benefit.

**DZ:** Yes. Just as Nrf2 protects normal cells, Nrf2 may also protect cancer cells from chemotherapeutic agents and facilitate cancer progression. Nrf2 is aberrantly accumulated in many types of cancer, and its expression is associated with a poor prognosis in patients. This is what I call the ‘dark side’ of Nrf2. Nrf2 and

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**Biography:** Donna D. Zhang, PhD, is a molecular toxicologist and oncologist at the University of Arizona. Her specialty is the Nrf2/Keap1 signaling pathway, and she has published over 86 peer reviewed papers, many on this pathway. In 1999 she received a DuPont Young Investigator Award, in 2006 she was the recipient of an NIH Outstanding New Environmental Health Scientist Award, and in 2012 she received the Society of Toxicology Achievement Award. She receives over 1,000 citations a year of her work with a total citation of over 6,000. She is currently the Principal Investigator for a study characterizing the anti-cancer properties of brusatol, an inhibitor of the Nrf2 pathway being tested as a possible adjunctive therapy in chemotherapy. She is also the principal investigator for a study on the protective role of Nrf2 in arsenic-induced toxicity and carcinogenicity. She is a member of the National Institutes of Health Review Committee on Chemo/Dietary Prevention, a reviewer for NIH, and is a member of the Distinguished Editorial Panel for Botanical Dietary Supplement Research Centers (BDSRC) and the Distinguished Editorial Panel for Centers for Advancing Natural Products Innovation and Technology Centers (CANPIT).
its downstream genes are overexpressed in many cancer cell lines and human cancer tissues, giving cancer cells an advantage for survival and growth. Furthermore, Nrf2 is upregulated in resistant cancer cells and is thought to be responsible for both intrinsic and acquired resistance to chemotherapy. Therefore, it may actually be helpful to inhibit the Nrf2 pathway during chemotherapy.

**In Focus:** How do cancer cells manage to take advantage of Nrf2, and how does it help them?

**DZ:** Many cancer cells carry a mutation in Nrf2 or Keap1, which diminishes the ability of Keap1 to keep Nrf2 destroyed. Thus, Nrf2 is constitutively overexpressed at maximal levels. With all that extra Nrf2 to protect them, these cells are more resistant to chemo- and radiotherapy. When we downregulate Nrf2, the cells are more susceptible to anti-cancer drugs.

**In Focus:** Does that mean that an individual who has cancer should not be eating healthy, Nrf2 promoting foods and dietary compounds?

**DZ:** It get this question quite often after I give a talk. My answer is, no. Diet is a gentle and intermitent stimulant of Nrf2, and your diet wouldn’t really impact the cancer cell, because the cancer cell has evoked a somatic mutation so that Keap1 is no longer effectively binding to Nrf2. Nrf2 is continually upregulated in the cancer cell. So in those cancer cells, Nrf2 is always there, always highly expressed. Eating Nrf2 stimulating foods in your diet would not further upregulate Nrf2 levels in cancer cells at all.

**In Focus:** That’s good to hear. So tell us about your work on inhibiting Nrf2 in the cancer cell.

**DZ:** Our laboratory has developed the first Nrf2 inhibitor in the world, called Brusatol. We have been working on it since 2005. In our studies, it appears to be really great for sensitizing cancer cells to chemotherapy, and may eventually prove an effective adjuvant to enhance chemotherapy. We aren’t at the stage of a clinical trial yet, but we have shown it works beautifully in mice lung cancer models.

**In Focus:** What is your final message?

**DZ:** Eat your broccoli or other tasty foods and spices that we have discovered are Nrf2 inducers, from cinnamon to carrots!

**Selected Recent Bibliography**


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In Focus: What got you interested in studying broccoli?

Jeffery: I used to be a toxicologist and I got very interested in foods that stimulate detoxification enzymes in the liver. I actually sent a grant proposal to the USDA to study Brussels sprouts, but the grant was turned down, as they said too few people eat Brussels sprouts. So I changed the vegetable to broccoli, and they funded the study. And ever since I’ve been fascinated by broccoli. It’s such an easy vegetable to eat. It’s becoming more and more popular. It’s one of the most effective cancer-preventing vegetables there is, both because of its levels of Indole 3 carbinol and sulforaphane. It also accumulates selenium.

In Focus: What have your studies revealed about eating broccoli raw, versus steamed, microwaved, or cooked?

Jeffery: We’ve done numerous studies, and ultimately we’ve found that light steaming for 3-4 minutes is ideal. That releases enough of an enzyme that releases sulforaphane, without destroying it. Light steaming is more effective than eating raw broccoli, though of course I don’t want to tell anyone not to eat their broccoli raw. It’s still good for them raw. But steaming makes it even better. Many people boil their broccoli, but we found in a study earlier this year that the enzyme that releases the sulforaphane is destroyed within one minute of either microwaving or boiling. Steaming is far gentler.

In Focus: So boiled broccoli doesn’t do the trick? Not even when you digest it?

Jeffery: There is definitely a discussion going on in the scientific literature about whether the microbes that live in your lower gut could release sulforaphane for you. We did two small clinical studies to test that, with four male students in each study. None of them were able to form more than about 10% of the total possible amount of sulforaphane by eating boiled broccoli. However, if we gave them another food in the same family with the same enzyme that releases the sulforaphane, that helped. For instance, just eating a side dish or salad with wasabi, or radish, will help release sulforaphane from your broccoli.

In Focus: What about frozen broccoli?

Jeffery: We have been worried about frozen broccoli, since so many people seem to be buying and cooking it. So we are study-
From NO/ONOO- Cycle to Nrf2: A Remarkable Bridge
An Interview with Martin Pall, PhD, about NO/ONOO- and Nrf2

Introduction: Martin L. Pall, PhD, is Professor Emeritus of Biochemistry and Basic Medical Sciences at Washington State University and widely known for his novel theory, dubbed NO/ONOO- cycle (pronounced no-oh-no!). In the cycle, which is based on 34 well-documented mechanisms, elevated levels of nitric oxide (NO) and its highly damaging metabolite, peroxynitrite (ONOO-), are at the crux of a runaway cycle of free-radical damage in which inflammatory molecules are chronically elevated and we have mitochondrial dysfunction as well. Peroxynitrite initiates a complex biochemical vicious cycle, known as the NO/ONOO- cycle, which is responsible for many chronic inflammatory conditions. Pall developed a highly specific and effective antioxidant protocol, called The Pall Protocol, to help reverse the NO/ONOO- cycle and restore health and immune balance. Here, he discusses the remarkable and wholly unexpected bridge he discovered last year between the NO/ONOO- cycle and Nrf2, along with his own dietary choices. His review article on Nrf2 appeared in Acta Physiologica Sinica in February of 2015.1

Selected Bibliography

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In Focus: You’ve published 31 papers and a 16 chapter book on the NO/ONOO⁻ cycle and related topics. What led you in a different direction, to Nrf2?

MP: The two are actually deeply connected, something I learned when I published a paper suggesting the NO/ONOO⁻ cycle plays a central role in heart failure. That was 2013.² But there were a few aspects that still puzzled me, and one was how peroxynitrite inhibited the cyclooxygenase (COX) pathway. The COX enzymes trigger the production of inflammatory molecules such as prostaglandins, and though they are critical for many functions they can also be involved in chronic inflammatory states. And as I was hunting for an answer, I stumbled onto Nrf2. I discovered that the cyclooxygenase pathway actually raises the levels of Nrf2 in the cell. So I thought, let me look into Nrf2. I had no idea what was in store for me. I was completely blown away by what I found.

In Focus: Can you summarize what you discovered about Nrf2?

MP: Nrf2 does far more than raise endogenous antioxidants. It has highly significant anti-inflammatory effects. It improves mitochondrial function. It’s an incredibly important central node of regulation for the body, one where all these health promoting factors come together and produce wide-ranging responses to help protect us from essentially all the chronic inflammatory states. I said to myself, okay, if that’s the overall pattern I’d better look at the details to see how they play out. So I had a flurry of activity where I looked at about a hundred papers, and read about fifty of them in depth.

To me, the most exciting aspect of Nrf2 is its connection with the NO/ONOO⁻ cycle that I’d been working on for so many years. Nrf2 is how evolution helps us avoid NO/ONOO⁻ inflammatory conditions. I’ve published now on 23 different diseases that are linked in some way to NO/ONOO⁻. But a lot of those publications are necessarily somewhat superficial. My best, most detailed paper is probably the one on heart failure. I’m aware that critics of my theory often feel I’m over-reaching, and that NO/ONOO⁻ cannot possibly be involved in all those diseases. It sounds too wide ranging. That’s a reasonable response until you look more closely at the data. You discover that Nrf2 is this incredibly complex, highly evolved system that very effectively quiets the NO/ONOO⁻ cycle. You only get that kind of well-coordinated and highly evolved set of responses when nature has decided something is very important.

In Focus: What is the best

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Estimated Nrf2 Raising Nutritional Components in the Two Most Healthful Diets Known

<table>
<thead>
<tr>
<th>Nutrient component</th>
<th>Traditional Mediterranean Diet</th>
<th>Traditional Okinawan Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenolic antioxidants</td>
<td>High consumption from olives and olive oil, herbs, legumes, eggplant, many leafy green vegetables</td>
<td>High consumption from soy many green vegetables and herbs, also provided by purple sweet potato varieties, “Okinawan spinach”, and Perilla (major source of rosmarinic acid)</td>
</tr>
<tr>
<td>Carotenoids</td>
<td>High consumption especially from tomatoes and leafy green vegetables</td>
<td>Very high consumption from sweet potatoes and many leafy green vegetables</td>
</tr>
<tr>
<td>Long-chain omega-3 fatty acids</td>
<td>High consumption from fish; also purslane and walnuts provide fatty acid precursors to the human body</td>
<td>High consumption from fish; also leafy green vegetables provide some fatty acid precursors to the human body</td>
</tr>
<tr>
<td>Isothiocyanates</td>
<td>Probably average for European diets</td>
<td>High from cruciferous vegetables and daikon radish, but no higher than other East Asian diets</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>High from Mediterranean herbs, olives, peel of fruits and eggplant</td>
<td>Uncertain substantial levels in Perilla and some other herbs; may be high</td>
</tr>
<tr>
<td>Allium derived sulfur compounds</td>
<td>High consumption of garlic and onions</td>
<td>Relatively high (onions, other allium) probably similar to Chinese diet</td>
</tr>
</tbody>
</table>
way to use our insights into Nrf2 therapeutically?

**MP:** I always say Nrf2 is best used for preventing disease. We have less evidence that it can reverse disease, especially cancer, although we may find that it’s also very useful for treatment of many diseases. I think that diet, exercise and supplements are all useful. (Caveat, in some conditions, such as chronic fatigue syndrome, exercise may not be helpful.) So let me just point out something that nobody else has yet pointed out, to my knowledge. Three of the classes of nutrients that raise Nrf2 actually work through oxidation. Oxidative stress activates Nrf2, and some classes of nutrients actually produce low levels of oxidative stress. Those are the active phenolics, the fish oils and Omega 3’s, and the carotenoids. I think it’s important to use those groups specifically in treatment.

**In Focus:** If the carotenoids are so important, why do you think beta-carotene hasn’t panned out in supplements?

**MP:** I believe one reason is that people usually take synthetic beta-carotene. About half of the natural beta-carotene molecules contain a cis double bond, but the synthetic ones do not, so they don’t oxidize as easily. The synthetic molecules may not raise Nrf2 at all. That’s my hypothesis, at any rate.

**In Focus:** What are your favorite Nrf2 foods?

**MP:** I tend to eat things that I know have components that raise Nrf2. I eat a fair amount of carotenoids including tomatoes and tomato products, a fair amount of onions and garlic, a lot of herbs, and lately I’ve been eating many black olives. I also found a source of the purple sweet potatoes that are part of the famed Okinawan longevity diet. Purple sweet potatoes are high in phenolics (the anthocyanins that give them their deep purple color) and in carotenoids. So they’re very healthy. I also eat black rice with lots of phenolics, and Chinese broccoli, which has a slight tinge of bitterness but not if you cook it properly.

**In Focus:** Sounds delicious. So what is your takeaway on Nrf2?

**MP:** You have to pay close attention to what evolution is telling us. Nrf2 is a very complex, incredibly well coordinated response to protect us from oxidative/nitrosative stress, inflammation, mitochondrial dysfunction and toxic chemicals in the body. So evolution is telling us that survival, health and longevity depend on our ability to handle these challenges.

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ly diagnosed with diabetes. But, like a ghostly afterimage, eight million more diabetics lurk in the shadows: undiagnosed, walking around oblivious to their potentially deadly blood sugar problems. And globally, 371 million individuals suffer from diabetes, while 4.8 million die of diabetes every year.¹

Then there are the 86 million Americans with pre-diabetes. Pre-diabetes manifests as insulin resistance, hyperinsulinemia and hyperglycemia, and can lead to vascular dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of cardiovascular disease.² It is a pro-inflammatory, pro-thrombotic state. Obese people with metabolic syndrome have a 10-fold increased risk for diabetes and a two-fold increased risk for cardiovascular disease (CVD) relative to normal weight people without the metabolic syndrome.³ Normal weight people with metabolic syndrome have a four-fold increased risk for diabetes and a three-fold increased risk for CVD.³ Metabolic syndrome puts an individual at high risk of full-fledged diabetes, and at increased risk for ocular, renal, neurologic, cardiovascular and metabolic disease—as well as early death.⁴,⁵,⁶

Finally, there’s a number measured only in money. In 2012, when we last looked, the economic burden of diabetes and pre-diabetes exceeded $322 million.⁷,⁸

These numbers are powerful and sobering. But the number on a blood test or census doesn’t take into account the complex orchestration of sugar storage throughout your body. Diabetes impacts the blood vessels, heart, liver, pancreas, kidneys, muscles, brain and nerves. It takes place in broad strokes (when insulin surges out from the pancreas after we eat a meal, for instance) and in tiny molecular reactions at an individual cell’s insulin receptor.

What follows is an up-to-date look at the newest research into astonishing and novel mechanisms of nutrients, each of which works on different pathways to support stable blood sugar. With scientifically based nutritional intervention, we can actually shift our biology, and end up with more than a number: we can return to good health.

**Berberine lowers fasting blood glucose by nearly 26% with no adverse effects.**

Berberine, particularly in its hydrochloride (HCl) form, is emerging as a novel molecule to help treat diabetes and related cardiovascular dysfunction. New research has uncovered its surprising ability to impact blood sugar by working on the insulin receptor itself. It also has a potent impact on the cardiovascular system, lipids and the liver, suggesting that berberine is a potent oral hypoglycemic agent that also has beneficial effects for disorders tightly linked to diabetes.¹⁰

Astonishingly, a recent study found that berberine actually increases insulin sensitivity through activation of the insulin receptor itself (InsR).¹¹ It is working at the molecular level of the cell as a truly unique phytochemical. By enhancing InsR sensitivity, berberine increases the cell’s glucose consumption. It also up-regulates the expression of the InsR gene in the liver and muscle cells. Rather impressively, in studies of numerous cell lines, berberine increased InsR in all of them.¹⁵ In animal models, rats with type 2 diabetes were treated with berberine and showed lowered fasting blood glucose and fasting serum insulin, and increased insulin sensitivity. In a human study by the same researchers, ninety-seven patients with Type 2 diabetes were given one gram of berberine daily for two months and compared to patients taking either the drugs metformin or rosiglitazone. Berberine therapy (1 g/d for 2 months) lowered fasting blood glucose by nearly 26%, compara-
ble to that of the drugs, and with no adverse effects. Serum insulin levels dropped by nearly 30% in the berberine group, which indicates increased insulin sensitivity. The researchers looked at InsR protein expression on the surface of blood cells by using sophisticated flow cytometry, and found an astonishing 3.6-fold increase. That increase was directly correlated with the reduction in blood sugar.¹⁵

Prescription drugs for diabetics can have many adverse effects, depending on the class of drug implemented, including liver effects. Berberine lowers elevated liver enzymes. In fact, it turns out to be an appropriate intervention for hyperglycemic patients with liver problems. Thirty five chronic hepatitis patients with Type 2 Diabetes were given berberine for two months. Berberine significantly lowered fasting blood glucose in the patients, and at the same time, their elevated liver enzymes declined significantly.¹⁵

Berberine has a strong impact on carbohydrate and lipid metabolism, and a potent effect on the stability of blood glucose. In fact, berberine increases insulin receptor expression in cultured human liver cells and skeletal muscle.¹²

Studies of diabetic rats found their insulin levels and insulin sensitivity normalized when they were treated with berberine. The pancreatic islets (insulin producing cells) were atrophied in diabetic rats, but less pathological change was observed in rats treated with berberine. The study concluded that “berberine has a protective effect for diabetes through increasing insulin expression, b-cell regeneration, antioxidant enzyme activity and decreasing lipid peroxidation.”¹³

An impressive human study followed two groups of diabetics. The first contained 36 newly diagnosed Type 2 diabetics for three months. They received either berberine or metformin (0.5 g 3 times a day). Their glycated hemoglobin (a test that estimates the levels of blood glucose over 3 months), fasting blood sugar, postprandial blood sugar (after a meal) and their triglycerides were measured. All parameters improved significantly on berberine, and the drop in blood sugar was equivalent to that of metformin. In the second group, 48 individuals with poorly controlled Type 2 diabetes were given the same program and experienced improvement in all measures. In both groups, about a third of the patients experienced transitional gastrointestinal side effects.¹⁴

Berberine doesn’t just lower blood sugar. It improves lipid metabolism, which often goes astray in metabolic syndrome and diabetes. Here, too, it is uniquely effective as a phytochemical, acting on the LDL receptor in the liver, as well as other pathways.¹⁵ In a study of 91 individuals with elevated cholesterol (52 males and 39 females) 1,000 mg of berberine taken daily for three months lowered cholesterol by 18%, triglycerides by 28% and LDL by 20%. HDL (the good cholesterol) remained unchanged. Liver function was also improved. A control group, in contrast, showed no change.¹⁶,¹⁷

Finally, berberine lowers blood pressure in animal studies, and hypertension is another issue in metabolic syndrome and diabetes. Berberine acts on both the endothelium and the vascular smooth muscle through multiple cellular mechanisms.¹⁸,¹⁹ It also helps patients with acute coronary syndrome (ACS)—which is caused by plaque that ruptures, forms clots, and occludes vessels. ACS is usually treated with implantation of a stent to expand the occluded vessel, but stents can cause vascular injury and an inflammatory response, so prevention is a key strategy. Numerous studies have shown that diabetics with ACS have a worse outcome. This has been attributed, above all, to the fact that diabetes is a pro-inflammatory and pro-thrombotic state. In a recent study, 130 ACS patients receiving a stent were followed. 69 patients received standard therapy, while 61 were given standard therapy plus 300 mg of berberine three times a day for a month. In the berberine group, several important markers of inflammation declined significantly, helping
protect against the vascular injury caused by stent placement. Berberine clearly appears to be clinically useful for both diabetes and heart disease.\textsuperscript{20,21}

Truly, berberine, like its mother plant, is golden.

**Common Ash: The Liver’s Perfect Helper**

The liver choreographs the storage and manufacture (called gluconeogenesis) of sugar in the body. When we eat, the liver stores sugar as glycogen. Between meals and at night, the liver turns that stored glycogen into glucose (called glycolysis or glycogenolysis). It’s no surprise that a burdened liver becomes less efficient at managing glucose regulation, particularly in those who are overweight or suffering from the increasingly common fatty liver diseases.

The seeds and fruits of the common ash tree (Fraxinus excelsior) seem to have been crafted by nature to aid the liver in handling sugar. Long used by Mediterranean populations for their potent anti-hyperglycemia and anti-obesity effects, science now backs up folklore and reveals many, potent mechanisms of action. \textit{F. excelsior} contains potent molecules such as coumarins, which thin the blood and increase blood flow in veins; as well as secoiridoids, a class of plant chemicals that can be neuroprotective, hepatoprotective, cardioprotective, hypoglycemic, hypolipidemic, and antispasmodic.\textsuperscript{22} They also contain phenylethanoids, which can be hepatoprotective and antioxidant.\textsuperscript{23,24}

**Extracts of \textit{F. excelsior} seed display potent hypoglycemic and anti-hyperglycemic activity without affecting blood insulin concentrations.**

Extracts of \textit{F. excelsior} seed display potent hypoglycemic and anti-hyperglycemic activity in laboratory animals without affecting blood insulin concentrations. The seeds also appear to inhibit the kidneys’ reabsorption of glucose.\textsuperscript{20} In a 2011 study, laboratory mice were protected from weight gain, high blood sugar and high insulin by an \textit{F. excelsior} seed extract. Mice were fed a high-fat diet over 16 weeks plus \textit{F. excelsior} extract, and compared with low-fat and high-fat diet controls. Weight gain, fat deposition, fasting blood glucose, and fasting blood insulin were measured. Mice on the extract gained 32% less weight, and their fasting blood glucose levels were lowered by 76%. Plasma insulin levels dropped by 53%. Liver weight gain was reduced by 63% and fatty liver curbed by 66.67%. The researchers concluded that the extract protects against obesity-related fatty liver.\textsuperscript{26}

The seeds also activate receptors called PPAR-alpha (Peroxisome proliferator-activated receptors). PPAR-alpha is mainly present in the liver, where it is a master regulator of fatty acid oxidation.\textsuperscript{27} In a variety of mouse models, substances acting on PPAR-alpha receptors lower plasma triacylglycerides, reduce fat and decreases hepatic and muscle fat, improving insulin sensitivity and reducing glucose in blood.\textsuperscript{28}

In humans, \textit{F. excelsior} reduces the “post-prandial” jump in blood sugar (a rise that occurs after eating). In a 2009 study, a standardized extract of \textit{F. excelsior} seeds was given to volunteers in a double-blind, randomized, crossover design. Sixteen healthy volunteers were given either a gram of wheat bran (placebo) or a gram of \textit{F. excelsior} seed extract after consuming 50 grams of glucose. Blood glucose levels (“postprandial plasma glucose”) were measured at 0, 15, 30, 45, 60, 90 and 120 minutes after consuming sugar or placebo. Insulin levels were measured at 0, 30, 60, 90 and 120 minutes. The extract significantly lowered glucose at both 45 and 120 minutes.\textsuperscript{29}

Finally, in an unpublished study, 22 overweight individuals aged 50-80 were studied for a total of 7 weeks in a randomized, crossover, and double-blind nutritional intervention, with a one week wash-out period between two separate intervention periods of 3 weeks each. Experimental groups were administered 1 gram daily of either placebo capsules or capsules containing an extract from \textit{Fraxinus excelsior} L. seeds. The seeds significantly lowered the glucose “curve” (the speed and amount that the blood sugar rises). The researchers conclude: “The administration of an extract from \textit{Fraxinus excelsior} L.
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seeds in combination with a low calorie diet induced favorable effects in glucose homeostasis in overweight/obese subjects.”

Golden Oldies Offer up New Scientific Proof

Silymarin, from the herb milk thistle, is well known for its liver protective properties. It has been extensively studied for inflammation and as an adjunctive in cancer treatment, yet much less is known about its therapeutic effect on diabetes. It turns out that silymarin helps regulate glucose and protect against related liver and cardiac dysfunction.

In a four-month, randomized, double-blind clinical trial it proved highly beneficial in improving the blood sugar profile of Type 2 diabetics. The study looked at 51 diabetics, divided into two groups. The first group of 25 diabetics received 200 milligrams of silymarin 3 times a day, along with conventional therapy. The second group of 26 diabetics received a placebo. Each month the researchers tested for glycosylated hemoglobin (HbA1c), fasting blood glucose, insulin, total cholesterol, LDL and HDL, triglycerides, and liver enzymes such as SGOT (AST) and SGPT (ALT). Those on silymarin had a significant decrease in all but the “good” cholesterol (HDL).

Diabetic nephropathy is a leading cause of end-stage kidney disease. It is usually managed by trying to control blood sugar, blood pressure, fasting blood

Each combination of silymarin and berberine improves fasting glucose, total cholesterol, LDL, triglycerides and liver enzyme levels.

A combination of silymarin and berberine improves fasting glucose, total cholesterol, LDL, triglycerides and liver enzyme levels.

Like silymarin, resveratrol is widely known as a potent antioxidant, and particularly known for its cardioprotective effects. Its impact on diabetes is now emerging. A 2013 study found that resveratrol supplementation exerted strong anti-diabetic effects in patients with type 2 diabetes. Sixty-six individuals with Type 2 diabetes were randomly assigned to a group that received either a gram of resveratrol daily, or a gram of placebo. Body weight, blood pressure, fasting blood
glucose (FBG), hemoglobin A1c (HbA1c), insulin, insulin resistance, triglycerides, total cholesterol, LDL, HDL, and markers of liver and kidney damage were measured at the beginning of the study and after 45 days. Resveratrol treatment significantly decreased fasting blood glucose, HbA1c, insulin, and insulin resistance. HDL was significantly increased. Liver and kidney function markers were unchanged.\textsuperscript{35}

Resveratrol has also proved remarkably helpful in obese patients with Type 2 diabetes. In one 2011 study, 11 obese males received a daily dose of 150 mg resveratrol or placebo for 30 days in a double-blind crossover design. Significant improvements were seen in insulin sensitivity, blood pressure, metabolic rate, and fatty liver.\textsuperscript{36}

Resveratrol is thought to mimic the beneficial effects of caloric restriction on glucose regulation and health by activating sirtuins, a group of powerful enzymes that are key to maintaining cellular homeostasis. Sirtuins are increasingly being recognized for their role in diabetes, especially in protecting the heart. Caloric restriction leads to overexpression of sirtuins—and improved health and longevity. Increasing the cell’s store of NAD+, a molecule that is now at the center of a hotbed of anti-aging research, also stimulates sirtuin activity, and this may be the mechanism of action of resveratrol. Sirtuins influence glucose metabolism in the liver, pancreas, muscle and fat. There is evidence they can improve insulin sensitivity and mitochondrial function.\textsuperscript{37} In a 2014 study, resveratrol was shown to activate one of the many sirtuins and improve cardiac function and fibrosis in mice, as well as in heart cells in vitro.\textsuperscript{38}

**Vitamins, Minerals, and Diet Are Powerful**

Key vitamins and minerals bring up the rear guard in natural constituents that help maintain healthy blood sugar. Chromium, biotin (a B vitamin) and magnesium are all known to improve glucose regulation. In a recent study on 43 individuals with poorly controlled blood sugar in spite of medication, a combination of biotin and chromium picolinate led to significant improvement in the blood sugar curve, as well as reductions in triglycerides and LDL.\textsuperscript{39} In another study, 447 adults with poorly controlled Type 2 diabetes were given either a combination of chromium picolinate (600 micrograms) with biotin (2 mg), or a placebo. Both groups were given oral anti-diabetic medications as well, and followed for 90 days. Glycosylated hemoglobin (HbA1c), fasting glucose, and lipids were measured. HbA1c in the chromium picolinate/biotin group decreased by over 50% and fasting glucose levels were reduced in the entire chromium picolinate/biotin group versus placebo.\textsuperscript{40} In addition, niacin-bound chromium (known as chromium polynicotinate), has a positive impact on lipids and blood sugar. In one randomized, double-blind, placebo controlled study of 40 individuals with high cholesterol (total cholesterol 210-300 mg/dL), a combination of grape seed proanthocyanidin extract (GSE) and chromium polynicotinate (CP) was given for two months. It was significantly more helpful than placebo at lowering LDL levels.\textsuperscript{41}

Finally, magnesium is very well tolerated and effective in diabetes, and plays an important role in insulin sensitivity and homeostasis. When 50 patients with Type 2 diabetes were analyzed for fasting and post-prandial glucose, HbA1c and magnesium levels, serum magnesium levels were found to decline with rise in HbA1c levels and with duration of the disease.\textsuperscript{42} In other research, Type 2 diabetic patients show lower serum magnesium levels than non-diabetic patients.\textsuperscript{43} Not surprisingly, magnesium supplementation has beneficial effects on blood glucose, lipid profile, and blood pressure in patients with Type 2 diabetes. In a 2014 double-blind, placebo controlled study, 54 diabetic patients were followed for 3 months. They received either 300 mg of magne-
Though this highly restricted diet would be virtually impossible for most folks to follow long term, it does demonstrate the power of dietary change.

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32. Orozco LJ, Buchleitner AM, Gimenez-Perez G, et al. Exercise and physical activity, including brisk walking, compared with being sedentary. 46,47,48 Losing weight can substantially improve blood sugar control in Type 2 diabetes and prevent progression from prediabetes to Type 2 diabetes. This is shown in meta-analyses of trials that look at exercise, diet, and standard drug therapy. A profound change in diet can actually reverse Type 2 diabetes in as little as 2 weeks as a result of 14,45,46 4 weeks on a restrictive, low-carbohydrate diet. 600 calorie a day liver diet. Glucose output, liver and peripheral insulin sensitivity, and pancreatic beta cell function were measured. An age-, sex- and weight-matched group of eight non-diabetic participants studied. Blood glucose normalized in one week, and by the end of the study, all other measures had normalized as well. Though this highly restricted diet would be virtually impossible for...

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Diabetes is a silent killer. Undiagnosed pre-diabetics and diabetics have no idea they have blood sugar problems. They may have had uncontrolled glucose (blood sugar) for years before they go to the doctor with obvious symptoms (e.g. increased thirst, feet pain, wounds that don’t heal well, vision problems, etc.) In the early stages of diabetes, metformin is typically the drug of choice. It is easy to take, fairly well tolerated, and works well. As insulin resistance progresses, so do the medications that are initiated. Once the beta cells (insulin producing) of the pancreas become irreparably damaged, exogenous insulin is required—most often for life. If the glucose and insulin resistance is not controlled, end-organ damage occurs, such as nephropathy, neuropathies and retinopathies.

A more holistic and integrative approach to diabetes is far more effective at preventing and reversing the condition. Here are examples of some step-by-step guidelines.

- **Use glycated hemoglobin as a screening test, along with fasting glucose and insulin,** in any adult at high risk for diabetes (particularly those with metabolic syndrome). Glycated hemoglobin is sugar bonded to your hemoglobin, and is measured by a lab test called HbA1C. The results indicate the average level of blood sugar (glucose) over the previous 3 months. Though this test is commonly used by physicians to monitor active diabetes, it is also useful as a screening test for adults in pre-diabetes or at risk of diabetes. There is an increased risk of developing diabetes when the HbA1C levels are 5.7% to 6.4%. Normal is < 5.7%.

- **Use the c-peptide test when indicated.** C-peptide is a surrogate marker that tells us how well a diabetic on insulin is doing—whether their beta cells are still functioning well enough to use the insulin. If insulin is elevated and C peptide is normal, we know the pancreas is still working (when not taking exogenous insulin). If c-peptide is low, we can infer some pancreatic insufficiency, which is a much more perilous situation.

- **Educate your patients,** so that they understand that diabetes and pre-diabetes are a systemic phenomenon of impaired glucose tolerance (in part due to insulin resistance) which includes the liver and muscle, not just the pancreas and their beta cells. Both the liver and muscle store and release glycogen. Though the standard American diet (SAD) is a diet high in simple carbohydrates that are nutrient depleted and calorie-deficient, diabetes is a disease of insulin resistance. Although the liver and muscle have some capacity to store and release glycogen, patients become insulin resistant and the liver is not able to store glycogen (glycogenolysis). Once the liver gets glycogen depleted, the muscle cells are unable to store glycogen and glucose uptake decreases. As glucose uptake decreases, the pancreas makes more insulin and blood sugar rises.

Biography: Dr. Todd A. Born, ND is a naturopathic doctor, and co-owner and medical director of Born Naturopathic Associates, Inc., in Alameda, California. He is also Product Manager at Allergy Research Group, LLC, and a Thought Leader for the UK-based “Clinical Education,” a free peer-to-peer forum for clinicians sponsored by Nutri-Link, a subsidiary of Allergy Research Group. Dr. Born graduated from Bastyr University in Seattle, and completed his residency at the Bastyr Center for Natural Health and its thirteen teaching clinics, with rotations at Seattle-area hospitals. Dr. Born’s clinical focus utilizes integrative medicine to treat chronic disease and refractory cases, supported by the basic medical sciences, including physical medicine (osseous manipulation, craniosacral therapy, hydrotherapy and physiotherapy), botanical medicine, homeopathy, biotherapeutic drainage, Ayurveda, counseling, pharmacology, and diet and nutrient therapies.
Once at all. In fact, we may reach for the nearest comfort food—the cookie or potato chip at that point, highly refined, quick to act on key receptors and well known for compounding the problem.7

**Craft a lifestyle program.** Once our patients, and clinicians, understand the many causes and contributions to diabetes, we need to help them with a program of cognitive reframing, stress reduction, mindfulness meditation, regular exercise (whether walking, jogging, swimming, or sports, but must also include weight bearing exercise), and time off for play and rest—as well as dietary remodeling.

**Choose combination formulas of natural medicines.** Recognize that although nutritional interventions and supplements can provide powerful support to pre-diabetics and diabetics, many patients can suffer from supplement burnout if they have to take too many pills, too many times a day. Try to look for combination formulas that support many different systems in the body and work on different mechanisms, leading to a healthy blood sugar level without an onerous supplement schedule. These include liver support, nutrients and molecules that sensitize insulin receptors, molecules that help protect the heart, and much more. Try to lean toward supplements that work on many mechanisms at once (such as resveratrol and milk thistle).

**Keep abreast of new literature on supplements.** See accompanying article for the newest research on novel uses of safe supplements that impact blood sugar.

**A Quick Guide to the Essential Insulin Receptor**

The insulin receptor (InsR) is essential for the action of all important hormone—insulin—throughout our body. Like all cell surface receptors, it helps ferry messages from the outside of the cell to the inside. Binding of insulin to InsR in the liver, muscles, or fat activates multiple cellular pathways that cause glycogen synthesis and glucose uptake increase, as well as reducing the amount of glucose the liver and muscles put out. Via the InsR, the blood glucose can be quickly lowered, keeping the entire body stable and healthy. Type 2 diabetes is a hyperglycemic state characterized by insulin resistance in many tissues, particularly the liver, muscles, adipocytes, and pancreatic beta cells. Eventually the insulin resistance leads to pancreatic β-cell burnout, where the cells actually start to die. Individuals with insulin resistance have either decreased levels or absence of InsR expression, or the receptor fails to activate an important substance called tyrosine kinase, which triggers a series of important cellular responses. Clearly, the InsR is the supremely important eye of the tornado we call diabetes. Upregulating and optimizing the InsR and restoring its homeostatic capacity is a key goal when treating and reversing diabetes.

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Histamine is a natural molecule that, when in balance, is extremely important for maintaining health. It functions as a neurotransmitter, and helps regulate stomach acid, muscle contraction, brain function, and the permeability of blood vessels. It assists our immune system in defending itself against pathogens. Histamine is stored within special immune system cells called mast cells, along with a smaller amount that is stored in basophils. When the immune system is activated in response to foreign material entering the body, histamine is the first inflammatory molecule that is released, as a kind of call-to-arms. Our body metabolizes endogenous histamine via a naturally-occurring enzyme called Histamine N-methyl transferase (HMT). HMT appears to work on the histamine receptors in our body.

Histamine is also present in many foods and some food additives (such as tartrazine, sulfite, or benzoate). Cheese, alcoholic beverages, vinegar, fermented vegetables, soy sauce, processed meats, strawberry and raspberry, tomatoes, apricots, cherry, plums, and pumpkin are all common sources of dietary histamine. Other foods, such as egg white, seem to release histamine. Most healthy people can easily detoxify food sources of the molecule via an enzyme called Diamine oxidase (DAO). DAO breaks down excess dietary or gut histamine, and excretes the breakdown products through the kidneys into the urine.¹

However, if an individual is naturally low in DAO, eats too many histamine-rich foods at once, or suffers from an imbalanced gut microbiome that tends to produce excess histamine, he or she may experience diarrhea, headache, stuffy nose, asthma, hives, low blood pressure, tissue swelling and throat tightening, racing heart, anxiety, fatigue, and other unpleasant symptoms. In histamine-sensitive patients with reduced DAO activity, symptoms can take up to eight hours after ingestion of a food to appear, leading to chronically cycling symptoms that appear mysterious and disabling.²,³,⁴,⁵

Histamine intolerance is not a classical allergy, where the presence of an antigen, such as flower pollen, results in subsequent antibody (usually IgE) release plus the release of our own natural histamine, along with symptoms. Yet the rise of traditional allergies impacts histamine intolerance, by increasing the total load of histamine. The prevalence and intensity of pollen is on the rise in many areas, because of global warming and pollution. According to a 2010 report by the National Wildlife Federation, “Unchecked global warming will worsen respiratory allergies for approximately 25 million Americans. Ragweed—the primary allergen trigger of fall hay fever—grows faster, produces more pollen per plant, and has higher allergenic content under increased carbon dioxide levels. Longer growing seasons under a warmer climate allow for bigger ragweed plants that produce more pollen later into the fall. Springtime allergies to tree pollens also could get worse. Warmer temperatures could allow significant expansion of the habitat suitable for oaks and hickories, which are two highly allergenic tree species. Changing climate conditions may even affect the amount of fungal allergens in the air.”⁶ And as pollution increases, our allergies worsen, as well. Humans tend to produce more allergic responses in the presence of pollution, such as diesel fumes.⁷,⁸

No wonder that, these days, histamine excess and histamine intolerance are genuine concerns.
One simple answer may be a long-term, low-histamine diet. This can also be supplemented with DAO, available as an oral enzyme. DAO can be seen as a first aid treatment for people who are aware of their difficulty in successfully breaking down and eliminating endogenous and exogenous histamine, after suitable confirmation by blood and urine tests. However, many people present to their clinicians with a series of mild to moderate immune responses to environment and food selections that defy easy analysis and diagnosis. A trial with the enzyme DAO may prove to be a quick and economic way to determine if symptoms improve – further investigations may also then be ordered, as well as the start of a low histamine lifestyle.

DAO can even be taken by normal individuals before a very high-histamine meal (pizza, rich in tomatoes and cheese, along with red wine, for instance). In addition, since gut microbes can produce histamine, oral probiotics may help lower histamine intolerance. The probiotic Lacticobacillus rhamnosus, for instance, downregulates the Histamine 4 receptor. Thus, select probiotic bacteria might diminish histamine-mediated, mast cell allergy-related activation. A low histamine diet, DAO and proper probiotic supplementation may be very useful tools in the growing problem of histamine intolerance in a high-pollen, high-pollutant world.

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