

By Kerry Bone

Nrf2 Part One

We all know about antioxidants. They are the good things in our diet that protect us against the evils of damage caused by free radicals. However, recently in both scientific circles and consumer opinion there has been a rethink of the value of antioxidants, largely led by negative publicity from certain clinical trials (such as the one on beta-carotene).

Rethinking the value of antioxidants

This rethink was highlighted in a 2012 article in the industry newsletter *newhope360*:

“Antioxidants as an ingredient category have suffered from the ‘magic pill’ syndrome. In the past 15 years these ingredients have soared on promises that remain mostly unfulfilled, and crashed on doubts that were overstated.”¹

The author Hank Schultz goes on to write:¹

“More than a decade ago information about the damage that free oxygen radicals can do in cells was becoming fixed in consumers’ consciousness. In a society focused on the attainment of eternal youth, free radicals, which had been linked to premature aging, had become the new bogeymen. And new miracle molecules—antioxidants—were coming to the rescue, armed with the powerful weapon of high ORAC values. ORAC numbers (oxygen radical absorption capacity) began to be quoted on package labels. ... This quick climb to the top began to be clouded by wavering doubts. First, there was the question of the ORAC test itself. ... Then there is the *in vitro* versus *in vivo* question. It doesn’t matter how good the sponge might be if you can’t use it to clean your kitchen.” (The *in vitro* versus *in vivo* question means that not all results produced in test tubes, such as ORAC values, translate into meaningful effects in living bodies.)

But in scientific circles concerns over the value of antioxidants go much further than this. The key free radicals produced in the body (called reactive oxygen species (ROS) because they are based around oxygen) might sometimes exert beneficial effects. The discovery of ROS signaling (where free radicals trigger essential, healthy responses) has been verified as important in a variety of physiological functions, including glucose-stimulated insulin secretion and arming of defenses against invading micro-organisms.²

To add fuel to the fire, there are new doubts over the oxidative stress theory of aging mentioned above. This theory was first proposed by Harman in 1956: ROS inflict indiscriminate oxidative damage to cells that is not completely neutralized by antioxidants and/or repaired. Damage then builds up with time causing aging. “Despite the intuitive logic and vast support for this theory, a causal link between oxidative stress and the rate of aging has not been clearly established.”³

Ironically, at the same time there has been an intriguing new insight into how plant-based herbal chemicals (phytochemicals) exert their antioxidant activity in the body that completely blows away such negative concerns. It will also hopefully change the way you think about phytochemical antioxidants forever.

An unstated assumption of the antioxidant theory is that they are passive sponges of free radicals, often acting outside the cell because many of them, especially the herbal ones, cannot enter cells anyway because they are too large and/or insoluble in the cell membrane. So to gain any significant protection against damaging free radicals you need to take large (possibly unrealistic) amounts of antioxidants, and once they are inside your body you cannot control any potentially negative radical-scavenging effects, because they are just passive sponges.

Antioxidant protection lies within every one of our cells

A new discovery completely changes this flawed assumption. An entirely novel cellular mechanism known as the Nrf2/ARE pathway describes a targeted approach to antioxidant protection **within** each and every living cell in our bodies. This primordial pathway, fundamental to all animal cells, is a dynamic response induced by oxidative or chemical stress on the cell. It is a switch-on, switch-off mechanism, and most of the priming agents studied so far that facilitate its action have turned out to be...yes, you guessed it... natural plant chemicals. Most importantly, it is a mechanism that only turns on when we need it.

So what exactly is the Nrf2/ARE pathway? A transcription factor is a cellular chemical that causes the DNA of the cell to manufacture specific proteins. Which proteins are manufactured depends on the transcription factor. Nrf2 is such a factor that is normally anchored in the cell cytoplasm (that is, outside the nucleus where the DNA resides) by a molecule known as Keap1. Chemical stress on the cell disrupts the tethering of Keap1 to Nrf2, releasing it. The free Nrf2 then moves (translocates) to the nucleus and there binds to the antioxidant response element (ARE), inducing the new synthesis of a range of antioxidant, detoxifying, protective and anti-inflammatory enzymes.

Yes, that's right. Not just antioxidant activity is induced by the Nrf2/ARE pathway, but a whole range (more than 200) of beneficial genes is activated. Nrf2 activation enhances DNA repair, haem metabolism, removal and breakdown of toxins and glutathione synthesis. It activates detoxification, stabilizes proteins, strengthens cellular integrity and reduces the inflammatory response.

Key antioxidant enzymes are produced, including catalase, superoxide dismutase (SOD), thioredoxin, peroxiredoxin, sulfiredoxin, ferritin, metallothionein and haem oxygenase 1 (HO-1).⁴ Major phase II detoxifying enzymes are also triggered, including glutathione S-transferases (GSTs) and NAD(P)H: quinone oxidoreductase 1 (NQO1).³ "These functions likely represent only a fraction of the true function of Nrf2 activity, some of which are only beginning to be understood."⁵

A few years ago an Australian colleague Dr Christine Houghton wrote the following:⁶

“What really put antioxidants on the map was the 1969 discovery of the core antioxidant enzyme, SOD (superoxide dismutase) by Duke University Medical School researchers, Drs Joe McCord and Irwin Fridovich. Their landmark paper describing SOD and its extraordinary clinical potential was the catalyst which spawned a whole industry around ‘antioxidants’ as supplements. What McCord and Fridovich discovered was that the cell manufactures very powerful antioxidant enzymes, SOD, glutathione peroxidase and catalase and that these endogenous enzymes are catalytic in that they will quench a free radical and then recycle themselves and quench another and another and so on. What this means is that each antioxidant enzyme can quench literally billions of free radicals per minute. The reaction rate at which SOD quenches the superoxide radical has been measured at 2×10^9 free radicals per second. Compare this with any diet-derived antioxidant such as vitamin C where one molecule can quench just one single radical. Period! One single radical vs billions per minute!”

Harness the power of Nature to kickstart healing

And you can prime the production of these three key antioxidant enzymes inside your cell using the right herbal phytochemicals, where they are needed, and only when they are needed. The genius of Nature!

Surely harnessing such a powerful mechanism as the Nrf2/ARE pathway will have profound effects when it comes to maintaining health and managing disease. In fact, emerging research has already identified several important benefits of priming the Nrf2/ARE pathway to maintain health and prevent disease:

- healthy aging and longevity
- protection against cancer development
- protection against radiation
- benefits in diseases involving oxidative damage and inflammation
- potential benefit in diseases resulting from accumulated toxins, even heavy metals

Let’s revisit the oxidative stress theory of aging. Comparing different animals, we find that short-lived species have lower levels of Nrf2 together with nuclear binding activity, higher levels of Keap1, and lower production of the ARE enzymes. In other words, healthy longevity may not be so much about your exposure to free radicals, but more about how well-protected your cells are from free radicals by this pathway.³

Improving your Nrf2/ARE response could even protect you from contracting cancer, at least that’s what the experimental models suggest. In fact, most of the key phytochemicals known to prevent cancer in animal models of carcinogenesis are now thought to prime the Nrf2/ARE pathway as well. The combination of anti-inflammatory and antioxidant activity with detoxification represents a very powerful mechanism for resisting the cancer-causing potential of carcinogenic agents.^{7,8}

Nervous tissue is richly endowed with fat, and as a result is highly prone to free radical damage. Beneficial effects of Nrf2/ARE priming/activation have been suggested in neurodegenerative diseases including diabetic neuropathy,⁹ Alzheimer's disease,¹⁰ Parkinson's disease (PD),¹¹ and age-related macular degeneration (AMD).¹² HO-1 is a known neuroprotective heat shock protein/enzyme that, for example, protects against brain injury (from a stroke).¹³ In one study, cells from a biopsy of the olfactory mucosa had lower glutathione levels and detoxifying capacity in patients with PD compared with those from healthy control donors. These cells from PD patients were also in a state of oxidative stress due to higher levels of hydrogen peroxide. Significantly, activation of the Nrf2/ARE pathway restored those defective cells to normal.¹⁴

Positive effects of Nrf2/ARE priming have been suggested for lung diseases as well including in cigarette smokers and for asthma, pulmonary fibrosis and emphysema. Cardiovascular diseases, autoimmune diseases and diabetes are also in the list of diseases that might benefit.¹⁵ The lungs are the tissues in the body most exposed to oxygen because of their very high surface area, and often suffer greatly from damage by ROS.

In Part 2 of this article I will describe the key herbs/phytochemicals known to prime the Nrf2/ARE pathway. These are the true antioxidants of the future that you can benefit from right now

Nrf2 Part Two

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What are the key herbs/phytochemicals with Nrf2/ARE priming activity? The research has focused on just a few key ones: sulforaphane from broccoli (especially the sprouts), curcumin from turmeric, resveratrol, carnosol from rosemary, Ginkgo extract, the polyphenols from green tea, and the sulfur compounds in garlic.

Cruciferous cancer fighters

The consumption of cruciferous vegetables has long been associated with a reduced risk of cancer at various sites in the body. The key chemopreventative phytochemical sulforaphane is found in certain cruciferous vegetables and is especially high in broccoli sprouts.¹ It is believed to react with the cysteine amino acid residues in Keap1. As well as Nrf2-mediated induction of cellular defenses, many other mechanisms have been proposed for chemoprevention by sulforaphane and these appear to act synergistically.² Broccoli sprouts have reduced measures of oxidative stress in type 2 diabetes patients in a clinical trial.³

The spice connection

Rosemary contains the antioxidant molecules carnosol and carnosic acid. Both of these are now understood to be potent primers of the Nrf2/ARE pathway. For example, they have demonstrated neuroprotective activity by this pathway, which reflects on rosemary's

traditional use for memory.^{4,5} Recently a single 750 mg dose of rosemary improved the speed of memory and alertness of healthy older adults.⁶

Multiple animal lab studies have demonstrated the chemopreventative activities of curcumin and turmeric.⁷ The Nrf2/ARE pathway is thought to be an important basis for these effects. For example, the epigenetic silencing of Nrf2 during the progression of prostate tumors in a mouse model was reversed by curcumin.⁸ Brain and liver injury were reduced by curcumin through Nrf2-mediated induction of HO-1.^{9,10} Dietary curcumin led to increased Nrf2 protein levels and enhanced ARE binding in the liver and lungs of mice.¹¹

A significant proportion of the health-promoting activity of green tea and its key component EGCG is now thought to be via the Nrf2/ARE pathway.¹² These activities include chemopreventative, neuroprotective, detoxifying, and antioxidant outcomes. These beneficial effects for green tea are not seen in Nrf2-deficient animal models.

Resveratrol's powerful protection

Resveratrol is a highly active primer of the Nrf2/ARE pathway. Favorable Nrf2-mediated protection has been demonstrated in many body systems including the endocrine, cardiovascular, and nervous systems. For example, the endothelial (circulatory) protective effects of resveratrol against a high-fat diet were largely diminished in Nrf2 knockout mice.¹³

Cruciferous vegetables that contain sulforaphane

- broccoli sprouts
- brussels sprouts
- cabbage
- cauliflower
- broccoli raab
- bok choy
- kohlrabi
- kale
- collard greens

In a recent double blind, randomized, crossover study, 10 normal, healthy men and women were given a high-fat, high-carbohydrate (HFHC) meal (930 kcal) either with a placebo or a product containing 100 mg of resveratrol from *Polygonum cuspidatum* plus 75 mg of total polyphenols from a grape extract.¹⁴ The DNA binding activity of Nrf2 in white cells was significantly increased by $150 \pm 39\%$ over baseline at 3 hours after the meal and supplement intake, whereas meal consumption in the placebo group resulted in a significant reduction in Nrf2 binding activity at 5 hours. These were associated with a significant reduction of Keap1 by 48% in the supplement group and a significant increase by 66% in the placebo group.

Ginkgo deflects damage

Ginkgo is now well known as a powerful clinical antioxidant. Its antioxidant properties could play an important role in protection against radiation damage and appear to be mediated by Nrf2. In an uncontrolled trial conducted in 1995, Ginkgo extract protected against radiation-induced DNA damage in Chernobyl workers.¹⁵ More recently, the same

dose of extract (120 mg/day) protected against DNA damage caused by radioactive iodine treatment in patients with thyroid disease.¹⁶

There have been many trials of Ginkgo and stroke recovery in China and the *Cochrane Collaboration* published a systematic review and meta-analysis.¹⁷ While the review expressed concerns about the quality of most trials, it did find that Ginkgo was associated with a significant increase in the number of improved patients, based on neurological symptoms. Induction of HO-1 via Nrf2/ARE activation by Ginkgo has been suggested as a significant mechanism for neuroprotection and recovery following cerebral ischemia.^{18,19}

So this new understanding has the potential to provide us with herbs that can benefit health by:

- providing clinically relevant, safe, targeted antioxidant cover
- supporting antiaging/healthy longevity protocols
- supporting the detoxification of ANY toxin: drugs, alcohol, smoking, heavy metals, etc
- facilitating protection against ANY physical or biological stressor: especially radiation and heat stress
- reducing cancer incidence
- reducing cancer recurrence (but they are not to be used during chemotherapy or radiotherapy, see later)
- reducing neurodegeneration as in macular degeneration, Alzheimer's and Parkinson's diseases, stroke recovery and diabetic neuropathy
- acting as key moderators in any chronic inflammatory disease, such as osteoarthritis and autoimmune diseases
- acting as key preventative and palliative agents in cardiovascular disease, especially for arterial and endothelial damage/dysfunction
- helping to counter the negative metabolic effects of a high-fat and/or high-fried/food diet
- providing protective cover during weight loss
- improving metabolism in diabetes and metabolic syndrome
- supporting the lungs in any chronic lung disease

Why wouldn't you take these herbs every day? In fact, many of us do, either in our diets as supplements. I certainly do.

The 48-hour rule

There is just one cautionary note, Nrf2 and its downstream genes are over-expressed in many experimental cancer cell lines and human cancers, giving cancer cells an advantage for survival and growth. Also Nrf2 is upregulated in cancer cells resistant to chemotherapy and is thought to be responsible for acquired chemo-resistance. Therefore it may prove advantageous to inhibit the Nrf2/ARE pathway during chemotherapy.²⁰ There are still many questions to be answered. However, caution dictates that any known

Nrf2/ARE upregulating herbs should not be taken at least 48 hours either side of each chemotherapy or radiotherapy treatment, so the cancer killing effects of these treatments is not interfered with.

As a final reminder, the key herbs/phytochemicals identified by current research that are most active at priming the Nrf2/ARE pathway are: broccoli sprouts/sulforaphane and garlic, turmeric/curcumin, rosemary and green tea/EGCG, and resveratrol and Ginkgo.