**Discussion**

Nrf2 (NF-E2-related factor 2), a transcription factor in humans that is encoded by the NFE2L2 gene, regulates the expression of a set of antioxidant and detoxifying genes, protecting the body from the ravages of oxidative stress-related conditions, including (but not limited to) those affecting the brain and nervous system. In an unstressed state, Nrf2 is anchored in the cytoplasm by its specific inhibitor Keap1 (kelch-like ECH-associated protein 1). Keap1 functions as a sensor for oxidants and electrophilic xenobiotics. In the presence of any of these substances, Keap1 gives up its inhibition of Nrf2. This action stabilizes Nrf2, allowing it to accumulate in the nucleus and bind to the antioxidant response element (ARE) located in the enhancers of its target genes. Under this circumstance, Nrf2 then upregulates a variety of antioxidant enzymes and detoxifying proteins.*

A variety of natural substances have been shown to activate Nrf2:

- **Sulforaphane** (SGS), a naturally occurring isothiocyanate derived from cruciferous vegetables, induces phase 2 cytoprotective enzymes, supporting the body’s response to cellular insult. SGS may modify critical cysteine residues of Keap1, leading to Nrf2 stabilization and activation of the ARE and thereby inducing phase 2 enzymes. Research demonstrates that sulforaphane, through induction of Nrf2-dependent phase 2 enzymes, protects the brain against hypoxic-ischemic injury and may improve cognitive function when administered following traumatic brain injury.*

- **Pterostilbene**, a naturally occurring phenolic compound/analog of resveratrol that has comparatively better oral bioavailability, has been shown to possess cytotoxic, cytokine-inhibiting, and antioxidant properties. Resveratrol has also been shown to increase the protein and mRNA expression of Nrf2. There is evidence that Nrf2-mediated attenuation of oxidative stress and cytokine induction could be partially responsible for resveratrol’s potential effect on cell-life regulation. In rat and animal studies, resveratrol/pterostilbene have been shown to upregulate a significant number of genes involved in mitochondrial function as well as to modulate cholinergic neurotransmission and improve cognition.*

- **Curcumin’s** array of biological activities stems from its cytokine-balancing activity, antioxidant properties, and induction of phase 2 detoxifying enzymes such as heme oxygenase-1 (HO-1). Purification of curcumin yields the curcuminoids demethoxy curcumin (DMC) and bisdemethoxy curcumin (BDMC). DMC has been shown to induce HO-1 more effectively than curcumin. The ability of DMC and BDMC to induce the expression of HO-1 and to translocate Nrf2 to the nucleus of pancreatic beta cells in mice suggests that they may play a role in cellular defense. Human studies showed a significant increase in curcumin absorption when co-administered with BioPerine®, a patented black pepper extract.*

- **Green Tea’s** major polyphenol, (-)-epigallocatechin-3-gallate (EGCG), has been shown to induce expression of glutathione S-transferase, glutathione peroxidase, glutamate cysteine ligase, HO-1, and other enzymes, thereby protecting a variety of cells, including cultured neurons, against oxidative stress-induced cell death. EGCG modulates the redox-sensitive transcription factor Nrf2, which plays a key role in activating detoxifying enzyme HO-1 as well as other phase 2 enzymes.*

In summary, Nrf2 Gene-R8 is a promising approach to increasing antioxidant defenses by transcriptionally increasing the activity of the Nrf2/ARE pathway and positively affecting the transcription of damaging cytokine and antioxidant genes. Green tea, curcumin, and resveratrol (pterostilbene) have also been shown to influence amyloid formation; this influence further increases the potential of this innovative formula.*
Nrf2 Gene-R8™

Medicinal Ingredients (per vegetable capsule)
Broccoli (Brassica oleracea var. italica, Seed) ................................................................. 230 mg (30 mg Glucoraphanin)
Green tea (Camellia sinensis, Leaf) .................................................................................. 200 mg (75% Catechins, 45% Epigallocatechin 3-gallate, 3% Caffeine)
Curcumin (Curcuma longa - Root) ....................................................................................... 200 mg
Pterostilbene ......................................................................................................................... 50 mg

Non-Medicinal Ingredients
Hypromellose, calcium phosphate dibasic, magnesium stearate, stearic acid, silica, piperine, medium-chain triglycerides.

Recommended Dose
Adults: Take 1 capsule daily with food, or as directed by a healthcare practitioner. If you have difficulty swallowing capsules, break each capsule open and add the contents to a glass (240 ml) of water.
Consult a healthcare practitioner prior to use if you are pregnant, breastfeeding, or taking any platelet medication or blood thinners; or if you have gallstones, a bile duct obstruction, stomach ulcers, excess stomach acid, an iron deficiency, a liver disorder, or develop symptoms of liver trouble (such as abdominal pain, dark urine, or jaundice).
Consult a healthcare practitioner for use beyond 8 weeks.

Hypersensitivity to any of the ingredients.
Consult a healthcare practitioner prior to use if you are taking any prescription or over-the-counter medication.

References

Additional references available upon request