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 up-regulates 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 oxidative stress and inflammation. SGS may modify critical cysteine residues of Keap1, leading to Nrf2 stabilization and activation of the ARE, inducing phase 2 enzymes. Research demonstrates that sulforaphane, through induction of Nrf2-dependent phase 2 enzyme, 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, anti-inflammatory, 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 suppression of inflammatory response could be partially responsible for resveratrol’s potential chemopreventive effects. In rat and animal studies, resveratrol/pterostilbene have been shown to up-regulate a significant number of genes involved in mitochondria function, disruption of which is known to result in neurodegenerative disorders, and also to modulate cholinergic neurotransmission and improve cognition.*

**Curcumin’s** array of biological activities stems from its anti-inflammatory activity, antioxidant properties, and induction of phase 2 detoxifying enzymes such as Heme Oxygenase (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, hemeoxygenase-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 Activator is a promising approach for increasing antioxidant defenses by transcriptionally increasing the activity of the Nrf2/ARE pathway and activating transcription of anti-inflammatory and antioxidant genes. Green tea, curcumin, and resveratrol (pterostilbene) have also been shown to have anti-amyloidogenic properties that further increase the potential of this innovative formula.*
Nrf2 Activator™ Supplement Facts

Serving Size: 2 Capsules

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount Per Serving</th>
<th>%DV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucoraphanin (from broccoli extract) (Brassica oleracea italica) (seed) (SGS®)</td>
<td>60 mg</td>
<td>**</td>
</tr>
<tr>
<td>Turmeric Extract (Curcuma longa) (rhizome) (95% curcuminoids)</td>
<td>400 mg</td>
<td>**</td>
</tr>
<tr>
<td>Green Tea Aqueous Extract (Camellia sinensis) (leaf) (80% polyphenols, 60% catechins, 30% EGCG, 6% caffeine)</td>
<td>400 mg</td>
<td>**</td>
</tr>
<tr>
<td>Black Pepper Extract (Piper nigrum) (fruit) (BioPerine®)</td>
<td>100 mg</td>
<td>**</td>
</tr>
</tbody>
</table>

** Daily Value (DV) not established.

Other Ingredients: HPMC (capsule), stearic acid, magnesium stearate, dicalcium phosphate, silica, and medium-chain triglycerides.

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DOES NOT CONTAIN: Wheat, gluten, corn protein, yeast, soy, animal or dairy products, fish, shellfish, peanuts, tree nuts, egg, artificial colors, artificial sweeteners, or preservatives.

STORAGE: Keep tightly closed in a cool, dry place out of reach of children.

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DIRECTIONS: Take one to two capsules daily, or as directed by your healthcare practitioner.

Children, pregnant and lactating women, and individuals using blood thinners or receiving cancer treatment should consult their healthcare practitioner prior to use. Do not use if tamper seal is damaged.

DOES NOT CONTAIN: Wheat, gluten, corn protein, yeast, soy, animal or dairy products, fish, shellfish, peanuts, tree nuts, egg, artificial colors, artificial sweeteners, or preservatives.

STORAGE: Keep tightly closed in a cool, dry place out of reach of children.

EXCLUSIVE • PATENTED

All XYMOGEN® Formulas Meet or Exceed cGMP Quality Standards.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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Research References Available Upon Request