

# NRF2 Modulator

Supports the Body's Antioxidant Pathway\*



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NRF2 Modulator was formulated to help activate the Nrf2 pathway, which is the main regulator of the body's endogenous defense against oxidative stress and associated damage.\* This pathway regulates the production of important molecules that impart antioxidant activity, such as glutathione. It also regulates the production of detoxification enzymes and modulates the inflammatory response. NRF2 Modulator supports the activation of this pathway to promote redox balance and a healthy inflammatory response.\*

## Ingredient Highlights\*

- 300 mg of Curcumin C3 Complex® featuring three highly bioactive forms of curcumin standardized to contain 95% curcuminoids
- 250 mg of Vinia® Red Grape Powder providing the whole matrix of red grape nutrients and polyphenols
- 100 mg of Hytolive® Olive Fruit Extract (standardized to contain 10% hydroxytyrosol), a solvent-free extraction of olive polyphenols from the by-product water of olive oil production
- 50 mg of vitamin E isomers as DeltaGold® delta- and gamma-tocotrienols to protect against lipid peroxidation\*

## Nrf2 and Antioxidant Defense

The transcription factor nuclear factor-2 erythroid-related factor-2 (Nrf2) is a member of the Cap'n'collar family of basic leucine zipper proteins. It is a major sensor of oxidative stress and the master regulator of the cellular antioxidant response. Nrf2 plays an important role in the expression of approximately 500 genes involved in the coding of proteins that support redox balance, detoxification, stress response, and inflammation. The main regulator of Nrf2 is the Kelch-like ECH-associated protein 1 (Keap1). During times of being stress-free, Nrf2 levels are kept low and cytoplasmic Keap1 sequesters Nrf2. In conditions of oxidative stress, Nrf2 becomes free to translocate to the nucleus and activate target genes, such as heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1), and downstream regulators of redox balance and inflammation.<sup>1-6</sup>

**Curcuminoid powder, as Curcumin C3 Complex®**, is a patented, unique composition of three bioactive, health-promoting curcuminoids: curcumin, bisdemethoxycurcumin, and dimethoxy curcumin. These are the strongest and best-researched constituents of the turmeric root. Curcumin supports redox balance and promotes a healthy inflammatory response.\* A systematic review and meta-analysis of randomized controlled trials found that curcumin-containing supplementation significantly decreased markers of inflammation (interleukin-6 and high-sensitivity C-reactive protein) and oxidative stress (malondialdehyde), demonstrating potential anti-inflammatory and antioxidant properties.<sup>7</sup> One mechanism behind these actions may be that curcumin activates the Nrf2 pathway. Curcumin alkylates a protein thiol in the Keap1-Nrf2 binding complex, binding to cysteine 151 (Cys151) to activate Nrf2 and initiate its translocation to the nucleus to promote antioxidant gene expression.<sup>8-12</sup> It also may affect Nrf2 mediators and influence target genes.<sup>9</sup>

**Quercetin** is a dietary flavonoid that promotes a healthy inflammatory response and redox balance.\* Quercetin activates Nrf2 and downstream antioxidant activity including glutathione-related enzymes. The activation may occur by the p38 mitogen-activated protein kinase pathway, protein kinase C, and glycogen synthase kinase 3 beta.<sup>13,14</sup> Quercetin may also promote nuclear translocation of Nrf2 and Nrf2 phosphorylation.<sup>13,14</sup>

## Benefits\*

- Supports redox balance
- Promotes a healthy inflammatory response

## Supplement Facts

Serving Size 2 capsules  
Servings Per Container 30

Amount Per Serving	% Daily Value
Curcuminoid Powder (Curcumin C3 Complex®) (Curcuma longa)(rhizomes)(containing three curcuminoids: curcumin, bisdemethoxycurcumin, demethoxycurcumin) [standardized to contain 95% curcuminoids]	300 mg *
Red Grape Powder (Vinia®)(Vitis vinifera)(cells)	250 mg *
Quercetin	200 mg *
Olive Fruit Extract (Hytolive®)(Olea europaea)(fruit) [standardized to contain 10% hydroxytyrosol]	100 mg *
trans-Pterostilbene	100 mg *
Vitamin E Isomers (as DeltaGold® delta and gamma tocotrienols)	50 mg *

\*Daily Value not established.

**Other Ingredients:** Cellulose, quillaja extract, vegetable stearate, silicon dioxide.

A study on human aortic endothelial cells demonstrated that quercetin activated Nrf2 and downstream antioxidant enzymes including NQO1 and HO-1 to suppress lipopolysaccharide-induced oxidant production.<sup>15</sup> A rat study on doxorubicin (DOXO)-treated rats found that quercetin treatment increased Nrf2 messenger RNA expression and protected against DOXO-induced cardiomyopathy, including the reduction of blood pressure and left ventricular dysfunction.<sup>16</sup> A systematic review on quercetin treatment for sepsis determined that it attenuated inflammation and oxidative stress.<sup>17</sup> Another systematic review found that supplementation with quercetin led to a significant reduction in C-reactive protein levels in subjects who had chronic diseases.<sup>18</sup>

**Red grape powder (Vinia®)** is a complex of red grape cells from the red grape skin, flesh, pulp, and seed, providing the full spectrum of nutrients and polyphenols found in red grapes and wine. This includes the following polyphenols: resveratrol, tannins, quercetin, catechins, and anthocyanins. Polyphenols support the activation of the Nrf2 pathway to promote redox balance.\* Studies have found that resveratrol upregulates Nrf2 phosphorylation and blocks Keap1 to activate the Nrf2 pathway and downstream antioxidant gene expression.<sup>19-21</sup> Tannic acid has also been shown to protect against oxidative stress damage by activating the Keap1-Nrf2 signaling pathway.<sup>22</sup> Studies have demonstrated that anthocyanins likewise activate the Nrf2 pathway and downstream antioxidant and anti-inflammatory activity.<sup>23</sup>

Vinia® may promote redox balance and a healthy inflammatory response to support associated chronic diseases.\* One rat study found that consuming a red grape cell (RGC) powder attenuated increases in blood pressure, triglycerides, and insulin in rats with metabolic syndrome consuming a high-fat diet.<sup>24</sup> A clinical trial found that RGC consumption for 12 weeks led to an improvement in flow-mediated dilation and blood pressure, and also led to a significant decrease in lipid peroxidation compared to the placebo group.<sup>25</sup> A clinical trial also found that supplementing with RGC for 12 weeks led to a reduction in hemoglobin A1c and improved insulin sensitivity in patients with type-2 diabetes.<sup>26</sup>

**Olive fruit extract (Hytolive®)** is a 100% natural, patented ingredient that delivers the compound hydroxytyrosol. The hydroxytyrosol compound is a polar, phenolic phytochemical found in olive fruit, olive leaf, olive oil, and the by-products of olive processing. It supports redox balance and has the highest bioavailability and oxygen radical absorbance capacity, which is the oxidative measure of the olive oil components.\* Cell and animal studies have found that olive oil polyphenols, including hydroxytyrosol activate the Nrf2 pathway.<sup>27,28</sup>

**Trans-pterostilbene:** Pterostilbene is a naturally occurring phenolic compound and analog of resveratrol that has demonstrated cytotoxic, cytokine-inhibiting, and antioxidant properties.<sup>29</sup> In cell and animal studies, pterostilbene has been shown to activate the Nrf2 pathway to promote transcription of antioxidant genes, including NQO1 and HO-1.<sup>29-31</sup>

**Vitamin E Isomers (DeltaGold® delta- and gamma-tocotrienols):** Vitamin E supports antioxidant defense by protecting against lipid peroxidation and supporting cellular membrane integrity.\* Vitamin E, especially delta- and gamma-tocotrienols, activates the Nrf2 pathways.<sup>32</sup>

**Recommended Use:** Take 2 capsules per day or as directed by your health-care practitioner.

*For a list of references cited in this document, please visit:*

<http://www.designsforhealth.com/techsheet-references/nrf2-modulator-references.pdf>



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**\*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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