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Upregulation of phase II enzymes through phytochemical activation (Protandim) of Nrf2 protects cardiomyocytes against oxidant stress.

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Abstract Summary

Increased production of reactive oxygen species (cellular free radicals) has been implicated in the pathogenesis of **cardiovascular disease (CVD)**, and enhanced endogenous antioxidants have been proposed as a mechanism for regulating redox balance. Nuclear factor (erythroid-derived 2)-like 2 (**Nrf2**) is a transcriptional regulator of phase II antioxidant enzymes, and activation of **Nrf2** has been suggested to be an important step in attenuating oxidative stress associated with CVD. A well-defined combination (**Protandim**) of five widely studied medicinal plants derived from botanical sources has been shown to activate **Nrf2** and induce phase II enzymes through the antioxidant response element. The purpose of these experiments was to determine if treatment of cardiomyocytes with this phytochemical composition, marketed as **Protandim**, activates **Nrf2**, induces phase II detoxification enzymes, and protects cardiomyocytes from oxidant-induced apoptosis in a **Nrf2**-dependent manner. In cultured HL-1 cardiomyocytes, phytochemical treatment (**Protandim**) was associated with nuclear accumulation of **Nrf2**, significant induction of phase II enzymes, and concomitant protection against hydrogen peroxide-induced apoptosis.

The protection against oxidant stress was abolished when **Nrf2** was silenced by shRNA, suggesting that our phytochemical treatment (**Protandim**) worked through the **Nrf2 pathway**. Interestingly, phytochemical treatment (**Protandim**) was found to be a more robust activator of **Nrf2** than oxidant treatment, supporting the use of the phytochemicals (**Protandim**) as a potential treatment to increase antioxidant defenses and protect heart cells against an oxidative challenge.