

## The Protective Effect of Nrf2 Activation in Cardiovascular Disease

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### Abstract

The increased mortality of cardiovascular disease (CAD) has been linked with oxidative stress-related chronic inflammation. Current studies are focusing on the importance of reducing oxidative stress to improve outcomes in CAD. Atherosclerosis, a chronic inflammatory disease, has been documented as an underlying cause of myocardial infarction, stroke, and peripheral vascular disease. In this disease, low-density lipoproteins accumulate in the intima layer of the arteries and become oxidized by free radicals. Subsequently, free radicals cause endothelial and smooth muscle damage that is increased by cytokines released by foam cells. These factors are primary contributors to the development of chronic inflammation. Thus, current research is highlighting the significance of measuring and reducing oxidative stress as a fundamental approach to decreasing mortality in cardiovascular disease [1]. This paper reviews the protective effect of Protandim, an Nrf2 activator, in cardiovascular disease.

**Keywords:** Foam Cells; Free Radical; Reactive Oxygen Species; Oxidative Stress; Protandim; Respiratory Burst

### Abbreviations

CAD: Cardiovascular Disease; CAT: Catalase; LDL: Low-Density Lipoprotein; Nrf2: Nuclear Factor (Erythroid-Derived 2)-Like 2; ROS: Reactive Oxygen Species; GPx: Glutathione Peroxidase; SOD: Superoxide Dismutase

### Introduction

Free radicals and reactive oxygen species (ROS) are natural byproducts of cell metabolism. The endogenous antioxidant enzymes antagonize the proliferation of free radicals and ROS. Thus, their functional interaction creates a homeostatic balance. In a healthy state, the body produces a tractable amount of free radicals that can be neutralized by endogenous antioxidant enzymes. However, radiation, drugs, transition metals, and respiratory burst can increase free radical production. This resultant unbalanced state causes oxidative stress. The endogenous antioxidant enzymes glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) are vital elements for controlling free radical proliferation and oxidative stress. However, the daily increase of free radicals during pathological processes outnumbers the natural enzyme production of GPx, CAT, and SOD in the human body. Specific studies have shown that an increased intake of antioxidant-rich foods or antioxidant supplements minimizes the risk of free radical-related health issues [2]. Current research is fo-

cused on developing exogenous antioxidants to prevent disease, especially cardiovascular disease, Alzheimer’s disease, and cancer [1,3]. However, the exogenous supplementation of antioxidants is insufficient in the body’s battle against free radical damage. Thus, scientists continue to investigate ways to spur an endogenous antioxidants reservoir to counteract oxidative damage. To this purpose, nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activation is being investigated.

**Discussion**

Taguchi *et al.* (2011) highlighted the critical role of Nrf2 in reducing free radical proliferation via increasing endogenous antioxidant enzymes (Figure 1). They discussed that, under oxidative and electrophilic stress, Nrf2 becomes stabilized and translocated to the nuclei, where it activates target genes involved in the synthesis of antioxidant enzymes. They further determined that the target genes of Nrf2 are involved in the following pathways:

1. Glutathione synthesis: glutamate-cysteine ligase, catalytic subunit (Gclc); glutamate-cysteine ligase, modifier subunit (Gclm).
2. The elimination of ROS-thioredoxin reductase 1 (Txnrd1); peroxiredoxin 1 (Prdx1).
3. The detoxification of xenobiotics: NADPH dehydrogenase; quinone 1 (Nqo1); glutathione S-transferase (Gst) gene family.
4. Drug transport-multidrug resistance-associated protein (MRP) family [4].

The study of these pathways is essential to understanding how the body can contend with oxidative stress and inflammation.

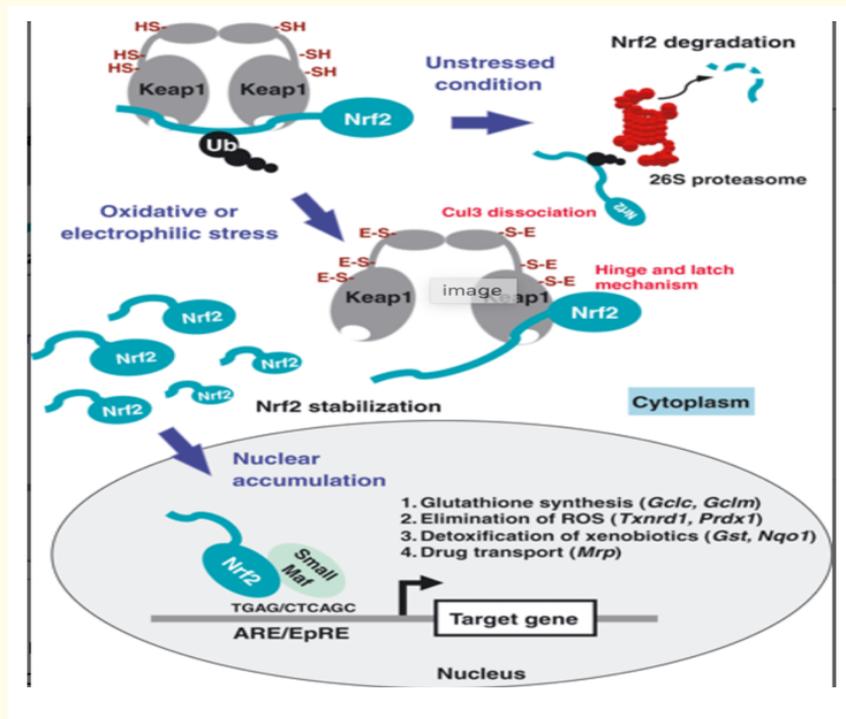


Figure 1: The Keap1-Nrf2 pathway. Taguchi., et al. (2011).

### Protandim, an Nrf2 activator

Protandim is a nutritional supplement composed of five natural elements: milk thistle (*Silybum marianum*) extract (225 mg), bacopa (*Bacopa monnieri*) extract (150 mg), ashwagandha (*Withania somnifera*) root (150 mg), green tea (*Camellia sinensis*) extract (75 mg), and turmeric (*Curcuma longa*) extract (75 mg). The synergistic formula of these natural compounds has been shown to decrease oxidative stress (measured by TBARS). It does so by directly stimulating Nrf2 activation and promoting an endogenous proliferation of the antioxidant enzymes (by naturally stimulating the body to produce more of the enzymes needed to reduce oxidative stress) and reducing the risk for inflammation and oxidative damage. Thus, the effect of Nrf2 activation may prove promising in enhancing specific protective factors in cardiovascular disease.

There have been numerous peer-reviewed studies [5-28] and several clinical trials completed since 2006 on the effect of Protandim; five of those studies focused on the effect of Protandim in CAD. According to Donoban *et al.* (2012), Protandim promoted Nrf2 nuclear localization and antioxidant enzyme expression, and protected human coronary artery endothelial cells from oxidative challenge [5]. Also, Reuland *et al.* (2013) demonstrated that the activation of Nrf2 resulted in a stronger response against oxidative stress in CAD [6]. They further concluded that the activation of Nrf2 by exercise could enhance the removal of damaged cellular components and mitochondria (mitophagy) [6].

In a study by Reuland *et al.* (2012), cardiomyocytes treated with Protandim resulted in a high activation of Nrf2 (different from the activation triggered by oxidative damage) that caused an increase in the antioxidant response to cardiomyocyte damage. The Nrf2 activation boosted the protection from oxidant-induced apoptosis [7].

A more recent study on the effect of Protandim on patients with severe proliferative pulmonary hypertension (PAH) found that the “treatment of Su/Hx rats with Protandim (in which Nrf2 upregulated the expression of the genes encoding antioxidant enzymes) protected against right heart failure without affecting angioobliterative PAH” [8]. The researchers of this study proposed continuing the investigation into the effects of antioxidant therapy in lung remodeling and right heart failure [8].

### Conclusion

The American Heart Association and several universities in the United States have studied and found favorable results with the use of Protandim, Nrf2 activator, in cardiovascular disease. These scientific investigations are fundamental steps in the development of noninvasive, preventative measures to protect the human heart against oxidative stress, thereby reducing CAD-related mortality. As exogenous antioxidant supplementation may be harmful or lack effective outcomes, it is suggested that future research focus on the activation of Nrf2 and endogenous antioxidant enzymes [29].

### Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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