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Nrf2 Pathway and the Reduction of Oxidative Stress

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ABSTRACT

Oxidative stress has been linked to cellular damage initiating disease processes such as cardiovascular disease, diabetes, and cancer. The Nuclear factor erythroid-derived 2 (Nrf2) pathway (Figure 1) aids in age-related cellular decline. The purpose of this study was to define the relationship between Protandim, its activation of the Nrf2 pathway, and decline in oxidative stress and cellular damage. The literature review included journal articles obtained from PubMed, Google scholar, and Cochrane review within the past 5-10 years, and contained both animal and human studies. The methods used in the animal studies included ANOVA, the standardized t-test, and the Neuman-Keuls post-test. P<0.05 was considered statistically significant. The human study included healthy participants, both male and female, age 29-78 with or without a specific medical diagnosis. Statistical analysis was based on the standardized t-test with a value of p<0.05 considered statistically significant. Liu et al. (2009) conducted a study investigating Protandim's ability to suppress cancer tumor formation. Tumor incidence declined by 33% and multiplicity of skin tumors by 57% with p = 0.003. Superoxide dismutase increased 35%, catalase 58%, and manganese superoxide dismutase 21%. In 2013, Reuland et al. conducted a study to determine if Protandim could activate the Nrf2 pathway and induce antioxidant enzymes, thereby protecting cardiomyocytes from apoptosis. Results indicated that treated cardiomyocytes showed increased levels of Nrf2 nuclear accumulation, activation of endogenous antioxidant enzymes, and protection against cell targeted oxidative stress (p<0.05). Quereshi et al. (2010) completed a study to delineate if Protandim decreased oxidative stress through the Nrf2 pathway. After six months of supplementation, TBARS decreased by 48% (p=.006), and plasma osteopontin decreased by 57% (p=.018). In 2005, Nelson et al. conducted a study to determine if Protandim decreased cellular damage. After 30 days of supplementation, TBARS declined by 40% (p =0.0001), at 120 days, TBARS declined by 40-54% (p =0.002), and superoxide dismutase and catalase increased by 30% and 54% respectively. The results from studies indicate that Protandim's activation of the Nrf2 pathway increased endogenous antioxidant availability, resulting in decreased oxidative stress and age related cellular damage.

INTRODUCTION

- Cellular damage induced by oxidative stress can lead to vulnerability toward cellular aging and predispose cells to disease processes.
- Cells respond to oxidative stress by increasing their endogenous antioxidant capacity, thereby decreasing the effects of reactive oxygen species.
- This process is modulated by the nuclear factor erythroid 2-related factor (Nrf2) – Keap 1 pathway.
- Nrf2 upregulates a series of phase II detoxification and antioxidant genes, aids in cell survival, is anti-inflammatory, and assists in energy metabolism.
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- Prevention of oxidative stress by phytochemicals has been studied as an approach to treatment of several diseases.

STATEMENT OF THE PROBLEM

Studies are needed to show whether or not the nutritional supplement Protandim is effective in lowering overall cellular oxidative stress thereby decreasing risk for disease process.

RESEARCH QUESTION

In adult patients, does a diet containing the supplement Protandim compared to a diet not containing the supplement Protandim, lower overall cellular oxidative stress?

LITERATURE REVIEW

Keap1-Nrf2 Pathway

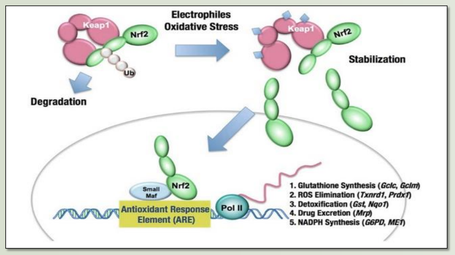

Figure 1. Keap1-Nrf2 Pathway. Under normal conditions, Nrf2 is ubiquitinated through Keap1 and degraded. Exposure to oxidative stress causes inactivation of Keap1. Nrf2 accumulates in the nucleus and activates multiple cytoprotective genes (Mitsuishi, Y., Motohashi, H., & Yamamoto, M. (2012).

- Nelson et al. (2005) found that Protandim decreased cellular damage. After 30 days of supplementation, TBARS declined 40% (p =0.0001), at 120 days, TBARS declined 40-54% (p =0.002).Superoxide dismutase and catalase increased 30% and 54% respectively (Figure 3).
- Liu et al. (2009) found that skin tumor incidence declined 33% and multiplicity of tumors declined by 57% (p=0.003). Superoxide dismutase increased 35%, catalase 58%, and manganese superoxide dismutase 20%.
- Robbins et al. (2010) concluded that Protandim suppressed DMBA/TPA induced cellular apoptosis.
- Quereshi et al. (2010) found that Protandim decreased oxidative stress through the Nrf2 pathway. After six months of supplementation, TBARS decreased 48% (p=.006), and plasma osteopontin decreased 57% (p=.018) (Figure 2.)
- Burnham et al. (2012) found that treatment with Protandim decreased TBARS (p<0.01).
- Donovan et al. (2012) found HCAEC treated with Protandim induced heme oxygenase (778% of control +/- 82.25 (p < 0.01), superoxide dismutase (125.9% of control +/- 6.05 (p < 0.01), NQO1 (126% of control +/- 6.5 (p < 0.01), and glutathione reductase (119.5% of control +/- 7.00 (p < 0.05).
- Mitsuishi, Motohashi, & Yamamoto (2012) outlined the pathophysiology of the Keap1-Nrf2 pathway.
- Reuland et al. (2013) found that Protandim treated cardiomyocytes showed increased levels of Nrf2 nuclear accumulation, activation of endogenous antioxidant enzymes, decreased cellular apoptosis, and protection against cell targeted oxidative stress (p<0.05).

DISCUSSION

Plasma TBARS: Protandim vs. Control Group

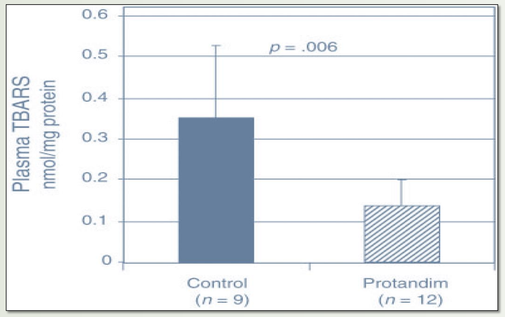

Figure 2. Plasma TBARS: Protandim vs. Control Group. Diets containing Protandim show a 48% decrease in plasma TBARS; 0.92 nmol/mg in controls (*n* = 9) versus 0.48 nmol/mg in Protandim® group (*n* = 12; *p* = .006) (Quereshi et al. (2010).

- Nelson et al. (2005), Quereshi et al. (2010), Burnham et al. (2012), and Reuland et al. (2013) conducted studies that resulted in decreased TBARS.
- Liu et al. (2009, Donovan et al. (2012), and Reuland et al. (2013) conducted studies that resulted in increased levels of antioxidants.
- Robbins et al. (2010), and Reuland et al. (2013) conducted studies that resulted in suppression of cellular apoptosis.
- Lie et al. (2009) conducted studies that resulted in decreased tumor incidence.
- Nelson et al. (2005), Liu et al. (2009), Quereshi et al. (2010), Robbins et al. (2010), Robbins et al. (2010), Burnham et al, (2010), Donovan et al. (2012), and Reuland et al. (2013) conducted studies that resulted in decreased levels of cellular oxidative stress.

Inhibition of Lipid Peroxidation

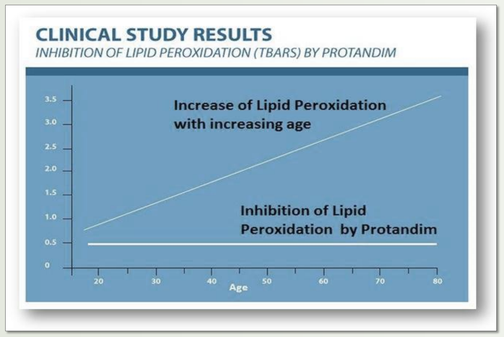

Figure 2. Inhibition of Lipid Peroxidation (TBARS) by Protandim. Human subjects before supplementation with Protandim showed an age-dependent increase in TBARS. The levels of TBARS dropped an average of 40% (p<0.0001) after 30 days of Protandim supplementation, and the age-related increase in TBARS virtually disappeared. (Nelson et al. (2005).

APPLICABILITY TO CLINICAL PRACTICE

- Cellular insult from reactive oxygen species is unavoidable. They are responsible for damage to cell membranes, DNA, and tissues. This damage can lead to premature aging and initiation of disease processes such as cancer, heart disease, neurodegenerative disease, and muscular disorders (Figure 4).
- Endogenous antioxidants are mediated through the Nrf2 pathway. Nrf2 also plays a role in regulation of survival genes.
- Scientific evidence has shown that Protandim induces the Nrf2 pathway, increases endogenous antioxidant production and provides cellular protection from damage due to oxidative insults.

Oxidative Stress and Disease

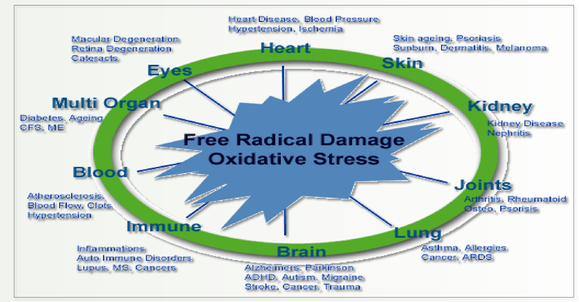

Figure 4. Oxidative Stress and Disease. Oxidative stress is a state is which free radicals overwhelms the body's antioxidant defense mechanism. This process has been implicated in the development of many diseases (Neurogenol, (2010).

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