A unique blend of natural compounds opposes age-related changes in gene expression related to dysregulation of cellular detoxification and antioxidant protection

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INTRODUCTION

Aging is associated with the accumulation of cellular toxins and damage. Declines in cellular detoxification mechanisms and impairments in antioxidant protection are consistently observed in aging models and likely contribute to age-associated accumulation of cellular damage. The master regulator, Nuclear factor erythroid 2-related factor 2 (Nrf2), is a transcription factor that regulates the basal and inducible expression of a large battery of genes encoding for cytoprotective factors including those that defend against electrophoretic stressors and oxidative insults.

The Nrf2/electrophile response element (EpRE) Antioxidant Protection and Phase II Detoxification pathways are impaired with aging due to age-related changes in gene expression (2). A key example is the reduction in glutathione (GSH) levels in all tissues with age due primarily to declines in glutamate-cysteine ligase and glutathione synthase expression (1). Opposing these changes in gene expression may delay or attenuate the aging process.

Most anti-aging intervention strategies to date, have tested single ingredients and have focused solely on an individual purpose of this study was to test a blend of natural compounds in middle-aged mice, compared to young mice, to determine if a blend of phytochemicals that opposes those age-related changes. It seems prudent to examine changes that occur during middle age rather than waiting until old age when an intervention may not be as impactful. Accordingly, the purpose of this study was to test a blend of natural compounds in middle-aged mice, compared to young mice, for the ability to oppose age-related changes in the expression of Nrf2-regulated genes involved in the detoxification of xenobiotics and xenobiotic metabolites and in the synthesis and regulation of intrinsic antioxidants and antioxidant enzymes.

METHODS

The phytonutrient blend was identified based on previous in vivo screenings of individual ingredients that positively influenced key cytoprotective pathways and included the following components:

- *Cordyceps sinensis*  
- Blood (red) orange extract  
- Pomegranate whole fruit extract  
- *Panax ginseng* extract  
- Broccoli seed extract  
- Grape seed extract

Data Analysis:

Full gene expression profiling was performed using Affymetrix Mouse Genome arrays in liver and gastrocnemius skeletal muscle tissues. Gene expression profiles and patterns were compared to identify changes in gene expression with age (MAC vs. YC) and in response to supplementation (MAS vs. MAC).

RESULTS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Liver YC vs. MAC</th>
<th>MAC vs. MAS</th>
<th>Gastrocnemius YC vs. MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nrf2</td>
<td>1.19 ± 0.00</td>
<td>1.23 ± 0.00</td>
<td>1.01 ± 0.07</td>
</tr>
<tr>
<td>NQO1</td>
<td>1.10 ± 0.00</td>
<td>1.11 ± 0.00</td>
<td>1.11 ± 0.14</td>
</tr>
<tr>
<td>GSTP1</td>
<td>1.09 ± 0.00</td>
<td>1.10 ± 0.00</td>
<td>1.10 ± 0.00</td>
</tr>
</tbody>
</table>

Figure 2. DNA Integrity. Changes in cytoprotective pathways responsible for maintenance of DNA integrity that are influenced by age (solid bars) and/or supplementation (hatched bars) in the liver. None of these pathways were changed in the skeletal muscle (data not shown).

SUMMARY & CONCLUSIONS

1. By middle age, expression of Nrf2 was downregulated in liver, but not in skeletal muscle, suggesting that either Nrf2 is not downregulated in skeletal muscle with age or that middle-age is too early to detect changes in Nrf2.

2. The phytonutrient blend effectively opposed the downregulation of Nrf2 in liver observed in middle-age controls.

3. In addition to restoring the expression of the master regulator Nrf2, the supplement opposed age-related changes in the expression of several Nrf2-regulated genes in liver and muscle, suggesting that it may combat some negative effects of aging.

4. Although many individual genes related to cellular detoxification were changed with age, none of the GO Pathways related to detoxification had changed significantly by middle-age indicating that these pathways decline at a later age.

5. Conversely, some pathways related to DNA integrity were changed by middle-age.

6. The supplement opposed most age-related changes related to DNA repair. In addition, the supplement upregulated some DNA repair pathways that had not changed by middle-age suggesting that by intervening at a younger age, the supplement may have stimulated protective mechanisms before they had the chance to decline.

7. These effects, elicited by a mid-life nutritional intervention, will likely have positive implications for healthy human aging or ‘youthspan’ and warrant further investigation.

REFERENCES:

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