What Dose of Resveratrol Should Humans Take?

By Dr. Xi Zhao-Wilson, PhD

In response to the many media reports about *resveratrol*, it seems like every supplement company is offering some form of grape complex for sale that claims to contain some resveratrol.

Recent attention has focused on a publication in the journal *Nature* that demonstrated improved health and survival in mice fed a high-fat diet supplemented with resveratrol, the same flavonoid that has been shown to increase the life span of a variety of organisms, including yeast, worms, flies, fish, and mice. This research tied the beneficial effects of resveratrol to mechanisms that underlie *caloric restriction*, and showed that such approaches could be used to treat certain chronic disorders and diseases of aging.

However, some popular press reports that accompanied this scientific article generated a fair amount of controversy, especially related to the dose used in the experimental mice and the estimated human-equivalent dose that may be required to exert the same biological effects. The *Life Extension Foundation*, however, is the only organization that has taken a grape-seed/resveratrol product already being used by health-conscious individuals and shown that the favorable biological effects of resveratrol can be achieved at a dose that is more than 10-fold lower than that used in the most-referenced study (referred to as the Harvard study).

Just recently, *Life Extension* reported that experimental animal studies conducted by BioMarker Pharmaceuticals were under way using the same grape extract fortified with resveratrol that is currently used by Foundation members. These studies were designed to evaluate the gene-expression response in mice fed resveratrol from the whole-grape extract found in the *Grapeseed Extract with Resveratrol* encapsulated product. The gene-expression data obtained from the grape extract group were compared to data from a group of animals subjected to caloric restriction. The preliminary data suggested a significant overlap in the favorable pattern of gene expression between the grape extract-fed mice and the calorie-restricted mice. In addition, experimental fruit flies (*Drosophila*) fed grape extract showed improvement in a model of Parkinson's disease, as well as an extended life span. These findings paved the way for further analysis identifying the specific molecular pathways involved in these effects. Here we provide an update to these earlier findings.

### Resveratrol and Other Health-Promoting Grape Constituents

The *Life Extension Foundation* constantly surveys the scientific literature in order to utilize the most important findings in promoting health and extending life. Mounting evidence demonstrates the broad-spectrum effects of biologically active molecules such as resveratrol, which is derived from natural plant extracts. In nature, molecular compounds like resveratrol are found in complex mixtures containing a diverse array of physiologically relevant molecules. Many of these constituents may be required in order to provide phytomedicinal agents with optimal bioavailability and synergistic action. Scientists must consider these points when conducting studies using either a single phytochemical (such as resveratrol alone) versus resveratrol combined with grape skin and grape seed extracts.

Classes of molecules found in natural whole grape, grape skin, and grape seed extracts include potent effectors like *proanthocyanidins* (in grape seed), *anthocyanins* (which give purple and red grapes their color), and single molecular entities such as *resveratrol* and *quercetin*. Scientific studies document the multiple health effects of these components, which can be characterized as antibiotic, anti-tumor, anti-diabetic, anti-ulcer, cardioprotective, anti-inflammatory, and anti-brain aging.

The cardiovascular health benefits of grape seed extract include favorable effects on blood pressure, enhanced endothelial function, and decreased oxidative stress. The potent antioxidant activity of grape seed extract may be responsible for its reported neuroprotective effects, as observed in animal models of Alzheimer's disease.

Recently, grape seed extract combined with calcium was found to be more effective than calcium alone in building healthy bone mass. Grape seed extract has effectively inhibited the growth of human colorectal tumor cells in the laboratory and in animals.

Recent findings on resveratrol's effects in experimental animal models are attracting a great deal of interest from the scientific community, while raising many questions about resveratrol's applications in humans. One of the most intriguing questions is what dose of resveratrol may help humans achieve the beneficial health effects that have been observed in animals. While extrapolating animal dosage to human dosage is difficult at best, scientists are using several approaches to address this question. The accumulating data from gene-expression studies in mice provide some clues. These findings are also helping to illuminate the molecular basis of the biological effects of resveratrol and grape extracts.

The Harvard Study generated a great deal of enthusiasm by showing that mice fed high-fat diets...
numerous diet-related health problems when supplemented with resveratrol. Compared to mice that were not given resveratrol, the supplemented mice exhibited increased survival, increased insulin sensitivity, decreased organ pathology, and increased numbers of mitochondria. Resveratrol was also responsible for shifting the gene-expression patterns of mice on the high-fat diet towards those of mice on a standard (moderate-fat) diet. These results were achieved by feeding the mice a daily resveratrol supplement equivalent to 22.4 milligrams per kilogram of body weight. In preliminary studies of this type, scientists often choose relatively high individual doses that are likely to generate an observable effect. Typically, more formal doseranging studies would be conducted later to identify optimal doses to attain specific effects. This is partly responsible for the controversy in the popular press regarding the relatively high dose of resveratrol used in this study.

While the Harvard study was under way, BioMarker Pharmaceuticals had already completed an eight-week controlled feeding study in which mice received either resveratrol (a synthetic version) or grape extract (containing resveratrol and other constituents), along with a “normal” diet. Gene-expression profiles were completed on these animals and compared to those of a group of calorie-restricted mice. Genes affected by either resveratrol formulation (synthetic or natural grape extract) or by caloric restriction were then compared. Importantly, the resveratrol dosage used in this study was much lower—approximately 12-fold lower—than that used in the Harvard study (see Table 1).

### Results of Gene-Expression Analysis

Mice on normal diets were fed a daily, relatively low dose of resveratrol obtained from either a synthetic source or from a whole-grape extract enriched with resveratrol. A control group of mice fed a normal diet without resveratrol supplementation and a calorie-restricted group were also evaluated. Total calorie intake was identical in the resveratrol, grape extract, and control groups, and 40% less in the calorie-restricted group.

At the end of an eight-week feeding schedule, the animals’ livers were harvested in order to prepare RNA (the biochemical cousin of DNA) for gene-expression profiling. The samples were specially prepared for analysis with DNA microarrays, or “gene chips,” containing a full set of characterized mouse genes (the Affymetrix GeneChip® contains a total of over 45,000 probe sets, representing a complete set of over 34,000 genes of the mouse genome). Gene-expression levels were determined using statistical methods that ensure a high degree of confidence in the data.

Both mouse groups that received resveratrol showed significant changes in the expression of key genes, confirming that even at the relatively low doses used in this study, there was a notable biological effect. The differentially expressed genes control over 100 different molecular pathways, including those related to metabolism (primarily metabolism of carbohydrates and lipids), DNA repair, and the regulation of cell death. Since the genes involved are in key biological pathways, they are likely to be responsible for at least some of resveratrol’s biological effects. Furthermore, significant results were achieved using a dose of synthetic resveratrol that was more than 10-fold lower than that used in the Harvard study.

Animals fed grape extract received resveratrol and other components of whole-grape extract. Their gene-expression response would therefore be expected to reflect effects of both resveratrol and other grape components. Genes that significantly changed in expression in the grape extract group are found in molecular pathways involved in carbohydrate metabolism and biosynthesis (such as the creation of blood sugars), and lipid metabolism and biosynthesis (such as the creation or reduction of cholesterol and fatty acids).

Interestingly, scientists noted a significant overlap—about 65%—when they compared the gene-expression patterns of the resveratrol and grape extract groups. While expected, these results confirm the similar effects of pure synthetic resveratrol and grape extract-derived resveratrol on gene expression in animals.

The gene-expression effects of “low-dose” resveratrol were similar to those seen in calorie-restricted mice: about 55% similarity between the calorie-restricted and resveratrol groups, and 52% similarity between the calorie-restricted and grape extract-supplementmed groups.

A method known as molecular pathway analysis can be applied to the gene-expression profiling results in order to identify the key regulatory pathways affected by the various treatments of resveratrol, grape extract, and caloric restriction. Displayed in Figures 1 and 2, these data show which pathways are specific to the different treatments, as well as pathways that are shared between or among the treatments.

Figure 1 shows the results for genes in pathways that are related to biological processes involving DNA; as shown by the overlap, 20 differentially expressed genes involved in DNA-related processes are regulated in the same fashion in animals receiving synthetic resveratrol,

### TABLE 1. RESVERATROL DOSAGE IN MICE

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DOSE (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard study* (high dose)</td>
<td>22.4 mg/kg/day</td>
</tr>
<tr>
<td>BioMarker study (low dose)</td>
<td>1.45 mg/kg/day, 1.74 mg/kg/day</td>
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</table>

a. Synthetic resveratrol
b. Grape extract resveratrol (obtained from Grapseed Extract with Resveratrol).
These data suggest that the three treatments share some common grape extract, or caloric restriction. These data are just a subset of the 10 genes involved in pathways controlled through gene expression. A similar approach was used to analyze genes involved in lipid metabolism. As shown in Figure 2, these genes involved in pathways related to lipid metabolism are commonly regulated by resveratrol, grape extract, and caloric restriction. These data are just a subset of the entire analysis. In total, 159 different molecular pathways were found to be commonly regulated by these three different treatments.

Resveratrol and grape extract produce strongly similar effects, based on the gene-expression responses demonstrated in mice fed a relatively low dose of these compounds. Comparison of these groups with calorie-restricted mice shows a significant overlap in the three treatments' regulation of similar biological pathways. These data add to the accumulating evidence that resveratrol triggers a biological response in mammals that is similar to that observed with caloric restriction, an intervention that is known to extend life span and protect against age-related diseases.2-5 These effects are observed even at a relatively low dose of resveratrol, indicating that a human-equivalent dose can be obtained through dietary supplementation with high-quality resveratrol products.

**What This Means to Aging Humans Today**

A fluid ounce of red wine averages around 90 micrograms of resveratrol.3 The resveratrol supplements used by Life Extension members contain 20 mg (20,000 mcg) of resveratrol in each capsule. Therefore, these 20-mg resveratrol supplements provide approximately 220 times the amount of resveratrol found in one fluid ounce of red wine.

Since a glass of wine is approximately 5 and 1/3 ounces, a person taking one 20-mg resveratrol supplement may ingest the equivalent amount of resveratrol found in 41 glasses of red wine. Needless to say, that is a lot of red wine.

In the studies conducted by BioMarker Pharmaceuticals, mice demonstrated favorable anti-aging gene-expression changes in response to receiving the human equivalent of 20 mg of resveratrol a day.

The very positive study results reported in the media in late 2006 used human-equivalent doses of resveratrol in the hundreds or thousands of milligrams a day. So what we have now are extremely favorable data on resveratrol (along with other grape constituents), with a wide range of probable optimal doses for aging humans to consider. Those who choose to consume 20 mg of resveratrol a day can take comfort in the BioMarker research showing that this potency exerted impressive changes in critically important genes involved in various aging processes and degenerative diseases.

Those who choose to consume higher doses of resveratrol can look at the media-reported studies that also showed very impressive results. The good news for consumers is that they can obtain standardized resveratrol and other grape constituents in 20-mg and 100-mg capsules, at a very moderate cost.

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**Footnotes:**

- Doses of drugs in experimental animals are often calculated in milligrams (mg) per kilogram (kg) of body weight. This enables the doses to be standardized among treatment groups.
- A threshold p-value of 0.001 for a minimum two-fold change in level of gene expression was used; this means that the probability that the gene-expression level is statistically significant is 99.9% or more.
- Polyphenolic acids, flavonoids, anthocyanins, and oligomeric proanthocyanidins.

**References:**
