

## Chapter 46

# Potential Benefits of Resveratrol Supplementation for Optimizing Health and Preventing Chronic Disease

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## ABSTRACT

Resveratrol is a polyphenol that has been researched extensively for its powerful antioxidant capacity. Recently, research from Harvard and other laboratories around the world revealed a different life-promoting mechanism found in this polyphenol that in December 2005 was front page news around the world. What these researchers had discovered was that mice fed resveratrol outlived similar mice by over 25%. Meanwhile, results of other studies carried out in France showed that mice fed resveratrol did not gain weight as compared to controls when given a high-fat and high-calorie diet. Beyond this, a number of studies have demonstrated resveratrol to have antioxidant, anti-cancer, anti-inflammatory, and cardioprotective properties.

A few human trials evaluating the effects of resveratrol and other polyphenols have been completed and numerous other trials are in progress to determine whether these same polyphenols will have benefits in humans. With unprecedented potential for health benefits and an extraordinary amount of media attention, resveratrol has grown to be a popular nutritional supplement. This chapter will discuss general information about polyphenols, with a focus on how resveratrol may improve human function. This discussion includes sources of resveratrol, benefits of resveratrol and the mechanism of action for these benefits, metabolism of resveratrol, safety issues, and information about commercial supplements.

**Keywords:** Anti-inflammatory, Antioxidant, Nutraceuticals, Polyphenols, Resveratrol, Supplements

## INTRODUCTION

Polyphenols are a specific group of plant products that have received considerable attention in recent years for their potential beneficial effects on health. There are over 8,000 different polyphenols found in the plant kingdom.<sup>1</sup> They are generally most concentrated in the skin of plants<sup>2</sup> and are often associated with protection from environmental stress, such as ultraviolet radiation.<sup>3</sup> The molecular structure of some polyphenols protecting plants from stress is very similar to molecules regulating genes which protect mammalian cells from stress. Thus, consuming these molecules which protect plants from stress may also have a beneficial effect on humans. This concept is termed xenohormesis.<sup>4</sup>

Polyphenols may be further classified into flavonoids, lignans, phenolic acids, and stilbenes.<sup>5</sup> While many polyphenols have been the subject of scientific research, some specific molecules have received considerable attention. These include tannins found in teas, quercetin found in grapes, and resveratrol, which is also found in grapes. Because of its recent popularity in the scientific literature, its potential for use in the medical world, and its emerging commercial availability, this chapter will focus on the use of resveratrol.

## RESVERATROL

Resveratrol, also known as 3,5,4'-trihydroxystilbene, is a stilbene found in grape skin.<sup>5</sup> It is best known for being found in high concentrations in red wine, but is also present in very small amounts in many other plant products.<sup>5</sup> It has been a very popular research topic since 1997<sup>6</sup> when it was first demonstrated to prevent cancer.<sup>7</sup> Since then, it has received considerable attention by researchers for its anti-inflammatory, anti-tumorigenic, and antioxidant properties, as well as its ability to increase lifespan in

mammals.<sup>8</sup> As of March 2008, an Ovid SP MEDLINE search revealed 2,009 hits for the term “resveratrol,” with 361 citations from 2007 alone.

Interest in red wine and its polyphenols is rooted in the French Paradox. This is based on the observation that the French population has a very low incidence of coronary heart disease, despite eating a diet high in saturated fats.<sup>9</sup> Researchers theorized that considerable red wine consumption provided a cardioprotective effect.<sup>9, 10</sup> This led to extensive research into the biochemistry of red wine components, and eventually resveratrol emerged as a key protective polyphenol.<sup>11</sup>

While the French paradox may be regarded as a good generalization of the effects of long-term red wine consumption on cardiovascular health, the considerable variation in polyphenol content must be considered when interpreting the effects of wine consumption on health. Additionally, it must be remembered that the beneficial effects of red wine consumption may not be attributable to resveratrol alone, but rather the interaction of multiple polyphenols. Likewise, large doses of resveratrol, itself or compounded with other polyphenols, may affect health differently than actual red wine consumption.

One of the reasons resveratrol has received so much attention is due to the scientific evidence that it significantly extends lifespan in mammals. resveratrol has been demonstrated to increase lifespan significantly in common laboratory models, including *S. Cerevisiae* yeast, *Drosophila Melanogaster*, *C. Elegans*, *N. Furzeri*, and laboratory rats.<sup>6</sup> In one of the most groundbreaking nutritional supplementation studies to date, rats were assigned to one of three conditions: control diet, high fat diet, and high fat diet with resveratrol. Rats that received the high fat diet alone demonstrated greater disease and decreased lifespan, as expected. Rats fed a high fat diet with resveratrol lived the same duration as the rats fed a control diet and had less evidence of chronic disease.<sup>8</sup> If this holds true for humans, resveratrol holds the potential not only to help humans live longer, but also healthier.

Unfortunately, it will be many years before there is sufficient data to determine if resveratrol or other polyphenol supplementation improves lifespan in humans. Nonetheless, widespread media attention about the potential benefits of resveratrol and other polyphenols has made them popular supplements in the general population. Therefore it is important for clinicians to understand the science of resveratrol and similar compounds and their potential applications. This chapter is intended to be a concise resource for clinicians, whereas the information in Maroon's book, *The Longevity Factor: How Red Wine and resveratrol Activate Genes for a Longer and Healthier Life*<sup>12</sup> is targeted at the mainstream population.

### **Sources of Resveratrol**

Red wine is known for being the most common source of resveratrol, with concentrations of up to 14 mg·L<sup>-1</sup> in Pinot Noirs.<sup>6</sup> While resveratrol is found in red wines, its concentration varies between and within each type. This is dependent upon the type of grape used, the region of the world where it is produced, and various environmental factors which may vary from year to year.<sup>13</sup> Indeed, this variation is not limited to resveratrol alone, but rather all polyphenols found in red wine.<sup>13</sup> White wines generally have less than 0.1 mg·L<sup>-1</sup> with a few exceptions having up to 2 mg·L<sup>-1</sup>, demonstrating the importance of grape color.<sup>6</sup>

Grape juice does contain resveratrol, with concentrations of 0.5 mg·L<sup>-1</sup> in red juices and 0.05 mg·L<sup>-1</sup> in white juices.<sup>6</sup> Whole grapes themselves do not have high concentrations of resveratrol, with a maximum of 3.54 µg·g<sup>-1</sup>, demonstrating the importance of the concentration of polyphenols within the skin.<sup>6</sup> While resveratrol is often reported to be present in peanuts (a maximum of 1.92 µg·g<sup>-1</sup>) and other plant products, the amount is almost negligible compared to that in wines.<sup>6</sup> One notable exception to this is the herb *Polygonum Cuspidatum*, which has a resveratrol concentration of 0.524 mg·g<sup>-1</sup>.<sup>6</sup>

With the information above considered, individuals who hope to benefit from resveratrol cannot simply eat grapes or most other resveratrol-containing products besides red wine. Therefore, a number of resveratrol supplements have been developed, with capsules containing anywhere from 1mg through to as much as 1g per dose. These supplements are discussed separately in a later section.

### **General Mechanisms of Action**

This section is designed to give an overview of the general mechanisms behind some of the benefits of resveratrol, as a complete analysis of its potential benefits from the thousands of relevant publications is beyond the scope of this chapter. Resveratrol has received special attention because it has been found to be the most potent activator of *SIRT1*, a gene critical to aging.<sup>11</sup> *SIRT1* is one of the

key genes upregulated during caloric restriction, which leads to a number of biological adaptations to prolong lifespan<sup>14</sup>. Resveratrol's activation of the *SIRT1* gene affects a number of cellular processes.

Resveratrol decreases nuclear factor kappa B (NFκB) activation.<sup>15</sup> NFκB is located in the cellular cytoplasm and translocates to the nucleus upon activation<sup>5</sup> where it induces transcription of multiple pro-inflammatory genes such as TNFα, IL-1, and IL-8.<sup>1, 16</sup> Resveratrol's blocking action of NFκB also suppresses iNOS, COX-1 and COX-2 expression, as well as many other genes including multiple cell adhesion molecules.<sup>1, 6, 16</sup> Thus, resveratrol's anti-inflammatory effect is multifaceted. Cancer and other chronic diseases, such as diabetes are associated with chronic activation of NFκB.<sup>17</sup> This chronic activation causes muscle wasting and insulin resistance<sup>15</sup> as well as resistance to cancer chemotherapy.<sup>17</sup> Therefore, its inhibition of NFκB may reduce the effects of related chronic disease. Resveratrol's anti-inflammatory actions have been demonstrated to prevent, delay, or reduce the severity of chronic inflammatory disease in animal models.<sup>6</sup>

By acting as a *SIRT1* activator, resveratrol induces PGC-1α activity, which results in mitochondrial biogenesis in the heart, liver, brain, and skeletal muscle, although there is variation between tissues.<sup>18, 19</sup> PGC-1α enhances mitochondrial function and reduces oxidative stress.<sup>19</sup> With greater numbers of mitochondria in skeletal muscle, more oxygen can be delivered to the working muscle cells. This allows greater metabolic energy to be produced through oxidative phosphorylation and decreases oxidative stress on the muscle cells. The end result is improved exercise endurance performance. This has been revealed through rodent studies whereby resveratrol supplementation significantly increased treadmill running times.<sup>18</sup>

Resveratrol itself has antioxidant properties<sup>20</sup> and upregulates cellular mechanisms of oxidative resistance by inducing mitochondrial superoxide dismutase in human cells.<sup>21</sup> The cardioprotective effects of resveratrol and other polyphenols may be in part to their ability to decrease LDL cholesterol oxidation, and therefore the pro-inflammatory cascade that ultimately leads to atherosclerotic plaques.<sup>22</sup> This has been demonstrated using grape juice in animal<sup>23</sup> and human models.<sup>24</sup> There are a variety of other mechanisms by which resveratrol may provide cardioprotective effects at various plasma concentrations reviewed elsewhere.<sup>13</sup> These include mechanisms of increasing endothelial nitric oxide synthase (eNOS) expression in endothelial cells, suppression of platelet activity, activation of adenosine receptors, and general antioxidant properties.<sup>13, 16</sup>

In addition to improving physical function, resveratrol holds potential for protecting the nervous system. This has been demonstrated in lab animal models for Alzheimer's, Huntington's, and Parkinson's diseases, as well as animal models for stroke.<sup>25, 26</sup> In Alzheimer's, soluble β-amyloid protein sheets accumulate in the endothelial cells of the brain and inhibit eNOS.<sup>25</sup> Additionally, β-amyloid proteins promote *p53* activity in neural cells, which leads to apoptotic cell death. Resveratrol works on multiple metabolic pathways resulting in a net decrease in amyloid deposits. Its *SIRT1*-inducing action represses *p53* activation, thereby preventing apoptosis, and also inhibits NFκB activation. This decreases the neurodegenerative toxins iNOS and cathepsin B, further protecting neural cells. Resveratrol promotes degradation of β-amyloid proteins. Additionally, resveratrol's antioxidant activity may block β-amyloid protein formation.<sup>25, 26</sup>

## **Results from Human Trials**

Much of the resveratrol literature has focused on *in vitro* and *in vivo* animal studies, with very few trials conducted on human subjects. However, the widespread news of resveratrol's potential to improve health and enhance life have led to a market for resveratrol supplements and interest from pharmaceutical companies for developing resveratrol-based drugs. The few studies describing its pharmacokinetics have demonstrated resveratrol supplementation to be very safe for humans,<sup>27</sup> as described in a later section. The continually emerging evidence suggests that resveratrol<sup>28-30</sup> and other similar polyphenols<sup>31, 32</sup> may indeed be beneficial to human health and performance.

A number of other studies have been performed on human cells. Trans-resveratrol has been demonstrated to prevent copper catalyzed oxidation in human LDL cholesterol by chelation.<sup>33</sup> In human lung epithelial cells, resveratrol has been demonstrated to inhibit IL-8, GM-CSF, iNOS, and COX-2.<sup>34</sup> In human alveolar macrophages, resveratrol decreases IL-8 and GM-CSF, further demonstrating its anti-inflammatory potential.<sup>35</sup>

Few trials have been performed to investigate the effect of oral resveratrol supplementation on antioxidant and anti-inflammatory markers in humans. Supplementation with grape polyphenols (in the

form of lyophilized grape powder), which included resveratrol, have been demonstrated to decrease markers of oxidative stress in postmenopausal women, as evidenced by decreased plasma TNF $\alpha$  and urine isoprostane concentrations.<sup>22</sup> Similarly, dealcoholized red wine supplementation has been demonstrated to reduce isoprostanes in male smokers.<sup>36</sup> Recent studies have demonstrated resveratrol to significantly lower IL-8 and F2-isoprostanes in healthy subjects following exercise,<sup>28</sup> further supporting its anti-inflammatory properties and abilities to reduce oxidative stress.

There is evidence that resveratrol may improve endurance performance and neurocognitive performance in humans. Healthy sedentary adults receiving oral mixed polyphenol supplements with resveratrol demonstrated significantly improved cardiovascular efficiency during exercise and increased verbal memory.<sup>29, 30</sup> While further research is needed, these results suggest oral supplementation of resveratrol and other grape polyphenols may indeed be beneficial to humans.

### **Metabolism and Bioavailability**

Resveratrol is found as both *trans*- and *cis*- forms, with *trans*-resveratrol having the greater biological activity of the two.<sup>6</sup> Orally administered resveratrol is rapidly metabolized by glucuronidation and sulfonation in the intestinal epithelium and liver.<sup>16</sup> Resveratrol's bioavailability is similar in humans and rats, with maximum plasma concentrations reached within an hour following oral administration.<sup>27, 37, 38</sup> While high concentrations of resveratrol are often used in *in vitro* studies, beneficial effects have been demonstrated at a variety of plasma concentrations ranging from 10 nM to 1  $\mu$ M.<sup>13</sup>

In one recent study examining the safety of resveratrol, forty healthy volunteers were provided with up to 5 g of resveratrol orally, with no major adverse events.<sup>27</sup> Peak plasma resveratrol concentrations reached 0.3 to 2.4  $\mu$ mol·L<sup>-1</sup>, peak resveratrol 3-sulfate concentrations reached 4 to 14  $\mu$ mol·L<sup>-1</sup>, and peak monoglucuronide concentration reached 0.9 to 4.3  $\mu$ mol·L<sup>-1</sup> in humans.<sup>27</sup> The concentration of unmetabolized resveratrol is lower than the necessary 5  $\mu$ mol·L<sup>-1</sup> required for chemoprevention derived from *in vitro* studies. However, it is possible that the *in vitro* data do not represent the true concentration needed *in vivo*.<sup>27</sup> Additionally, the metabolites of resveratrol may also be metabolically active and responsible for some of the chemopreventive effects.<sup>27</sup>

Earlier studies with fewer subjects have had similar findings. In one study using six healthy humans found approximately 70% of orally administered resveratrol to be absorbed. When 25 mg was administered, very little unmetabolized resveratrol was present, but metabolite concentrations reached a maximal concentration of 2  $\mu$ mol·L<sup>-1</sup>.<sup>38</sup> Similar studies have found similar absorption, as evidenced by 16%<sup>37</sup> to 24.6%<sup>39</sup> of dose consumed recovered of resveratrol and its conjugates in urine within 24 hours. It is also worthwhile to note there is evidence that small amounts of resveratrol may accumulate over long periods of time to sufficient concentrations for its beneficial effects.<sup>40</sup>

### **Safety**

As with other supplements, an ideal dosage is needed to produce benefits and there is potential for excess dosages to cause adverse effects. Potential side effects have been suggested if megadoses of resveratrol are used. Excessive activation of the *SIRT1* gene has been associated with heart failure in laboratory animals.<sup>41</sup> High concentrations of resveratrol, quercetin, and kampferol have also been demonstrated to inhibit the uptake of folate from intestinal cells *in vitro*.<sup>42</sup> A few *in vitro* studies have suggested the estrogenic effects of resveratrol may increase breast cancer cell proliferation,<sup>43</sup> although numerous other studies have found resveratrol to inhibit breast cancer cells.<sup>44, 45</sup>

While there are no reports of side-effects in peer-reviewed journals, anecdotal reports of tendonitis, numbness, and anemia have surfaced online. These claims have been supposedly from individuals taking high doses of resveratrol, subjectively defined as greater than 500 mg.<sup>46</sup> This has been explained by resveratrol's ability to chelate copper,<sup>33</sup> which can alter collagen and nerve metabolism. At the time of publication, these reports did not seem to be from reliable resources and may be related to marketing lower dose products.

Despite these concerns, there is currently no scientific evidence for detrimental effects of resveratrol supplementation. No notable side effects were not reported in Boocock's results, which include dosages up to 5 g.<sup>27</sup> Additionally, no subjects in Smoliga's study<sup>30</sup> reported any side effects after three months of oral resveratrol and mixed polyphenol supplementation, though this did not exceed 400 mg daily. Lastly, it should be remembered that the large concentrations of resveratrol which produce deleterious effects in *in vivo* models may not even be possible to achieve through oral supplementation.

Clinicians must remember resveratrol is metabolized in the liver and excreted by the kidneys. Additionally, it is important to note that resveratrol is transported to tissues by plasma proteins, with albumin being a major transporter.<sup>47</sup> Therefore population with diseases in these systems, or those taking drugs which affect them, may potentially respond to resveratrol differently than completely healthy populations. Furthermore, resveratrol may affect the metabolism of other drugs.<sup>6</sup> While there are currently no known risks and therefore no specific recommendations in regard to this, clinicians should remain alert when these types of patients are supplemented with resveratrol in case previously unreported adverse events develop.

### **Commercially Available Resveratrol Supplements**

Resveratrol-containing supplements have become very popular in recent years. Marketing has benefited from the number of magazine and newspaper articles describing the beneficial effects of red wine and resveratrol. The uninformed consumer may be easily persuaded into thinking all products are alike, that one particular product is scientifically proven to be better or safer than others, or that more resveratrol is always better. Therefore, it is necessary for clinicians to remain up-to-date regarding the facts of commercially available resveratrol supplements.

There is a wide variety in dosages of resveratrol in commercially available supplements, ranging from 1 mg to 1 g per dose. There is also considerable variability in price, with a range of \$0.12 through to \$45 per 100 mg. In many cases, these supplements are presented as being equivalent to a specific number of glasses or bottles of wine. As discussed previously, the concentration of resveratrol and other polyphenols vary greatly, and therefore it is important to consider the absolute amount of these polyphenols, rather than the somewhat subjective “wine equivalent.”

In November 2007, an independent nutritional supplement analyst, ConsumerLab, published their results after evaluating over one dozen different resveratrol products. Their tests determined the concentration of resveratrol in the supplement (compared to the product label), its chemical form, heavy-metal contamination, and the supplement’s ability to break down for absorption. While most of the products contained the amount of resveratrol advertised, one product contained 58.2% of advertised, another 26.5%, and another less than 0.01% of labeled. This emphasizes the need to buy reputable products which have been independently evaluated and not to necessarily believe all advertising claims.

Some companies are honest in their advertising approach, stating that resveratrol has been found to have beneficial effects in lab animals and that supplementation may be beneficial to humans. However, many commercially available resveratrol products advertise claims which have not been scientifically demonstrated in humans, as of the time of this publication. Others have taken advantage of Sinclair’s work, claiming “Harvard studies” have proven their product to be effective. In some cases, the advertisement is spun such that it appears a company’s particular product is so good that Harvard researchers decided to study it. In reality, these companies are marketing their product based on the existing studies on resveratrol in general, rather than their specific product. Some resveratrol products have quoted their own “experts” and inappropriately cited peer-reviewed articles to mislead customers. This abuse of references emphasizes the need for clinicians to double check the references on resveratrol and other nutraceutical products, either directly or by consulting with an independent and unbiased expert in the field who knows the current scientific literature.

There remains controversy whether or not resveratrol should be a stand-alone product or if it should be formulated with other nutraceuticals, such as quercetin. Quercetin inhibits the metabolism of resveratrol in the liver.<sup>48, 49</sup> Because the different effects between resveratrol and resveratrol metabolites are not known,<sup>16</sup> it is not clear whether or not this is beneficial. Thus, some companies specifically advertise their product is superior because it does not contain quercetin, whereas others claim their product is superior because it does contain quercetin. Indeed, quercetin has been found to be beneficial to humans when supplemented alone,<sup>50</sup> and is found in red wine with resveratrol.<sup>13</sup> Until further research is performed, it will not be clear which type of product is ideal.

## CONCLUDING REMARKS

While there are thousands of published articles describing the many biological effects of polyphenols in cell cultures and laboratory animals, there is very little published information regarding the effects of resveratrol on living humans at the time of this publication. As of the time of publication, resveratrol appears to be a safe nutraceutical supplement suitable for the general population. There are no documented side effects or contraindications to its usage, though physicians should still remain alert in the event heretofore unknown problems do exist. It is also unknown if resveratrol supplementation can significantly increase lifespan in humans. However, animal research has demonstrated it to be a very beneficial compound with considerable potential in human medicine.

A considerable amount of further research is needed to determine the degree to which resveratrol can be used for treatment and prevention of cancer and other chronic diseases. It is expected that there will be numerous studies describing the effects of resveratrol and other polyphenols on human health and performance in the next few years. Clinicians are advised to remain current in the polyphenol literature as more information becomes available regarding ideal formulation and dosage.

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