

# Resveratrol Monograph

## Introduction

Resveratrol (trans-3,4',5,-trihydroxystilbene) is a polyphenol molecule found in many plant species including grapes, peanuts, cranberries, Japanese giant knotweed (*Polygonum cuspidatum*), and others. Polyphenols, including flavonoids, flavonols, catechins, and stilbenes are present in the human diet in plant materials, where they act as antioxidants and protect the plant from damage by bacteria, fungi, and ultraviolet radiation.

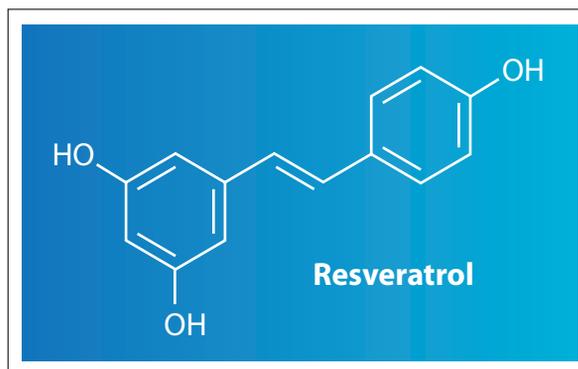
Resveratrol exerts anti-aging effects in animals. Numerous *in vitro* and animal studies have shown resveratrol has potent antioxidant and anti-inflammatory effects, promotes vascular endothelial function, enhances lipid metabolism, and has anticancer activity.

Since resveratrol is present in wine, it has been postulated that it might be the reason for the "French Paradox," the epidemiological phenomenon in which the French population has a significantly lower incidence of cardiovascular disease, even though the French consume a diet higher in fat than other populations.<sup>1</sup>

## Pharmacokinetics

Resveratrol is well absorbed; however, an important factor that appears to affect the bioavailability of resveratrol is the extensive first pass metabolism of this molecule in the small intestine and liver.<sup>2</sup> De Santi et al studied the metabolism of resveratrol in the duodenum and liver and found extensive sulfation and glucuronidation in these tissues.<sup>3,4</sup> This research group also found the flavonoid quercetin inhibits duodenal and hepatic glucuronidation and sulfation of resveratrol and may thus increase its bioavailability.<sup>3,5</sup> Others have demonstrated an eight-fold higher peak of sulfated resveratrol in the plasma compared to trans-resveratrol. Glucuronidated resveratrol plasma levels were three-fold higher than trans-resveratrol.<sup>6</sup>

A repeat-dosing study in four groups of 10 individuals, using six doses daily of trans-resveratrol at 25, 50, 100, or 150 mg for 13 doses, revealed a mean peak plasma concentration at 48-90 minutes after dosing. Considerable individual



variability in absorption was noted; however, a mean half-life of 1-3 hours was demonstrated after a single dose, and 2-5 hours after repeated doses.<sup>7</sup> Goldberg et al demonstrated a 30-minute peak concentration of resveratrol in humans after oral dosing.<sup>8</sup> In another study, quicker absorption was noted in doses taken without meals, and delayed absorption was seen when taken with a meal; however, total area under the curve, denoting the total amount absorbed, did not differ between groups.<sup>9</sup>

A study in mice showed, after a single oral dose of 14C trans-resveratrol, accumulation of radioactivity in the stomach, intestines, liver, and kidneys. Intact trans-resveratrol, as well as sulfur and glucuronide conjugates, were detected.<sup>10</sup>

A single-dose study in which 40 individuals were given one of four doses (0.5, 1.0, 2.5, or 5.0 g) demonstrated peak plasma trans-resveratrol levels at 1.5 hours. The mean peak plasma concentration of resveratrol ranged from 73-539 ng/mL (0.3-2.4 μmol/L) across the dose schedule.<sup>6</sup>

## Mechanisms of Action

### Antioxidant

It appears that resveratrol has numerous mechanisms by which it exerts its effects on the human body. As is the case with most dietary polyphenols, resveratrol exhibits antioxidant activity. Oxidative damage is proposed to be a component of numerous diseases, including cardiovascular disease and cancers. A study of resveratrol's antioxidant activity in human erythrocytes *in vitro* found resveratrol protected erythrocytes from hydrogen peroxide-induced lipid peroxidation, although to a lesser degree than the

polyphenols quercetin and pterostilbene (a di-methoxylated resveratrol analog). A synergistic antioxidant effect was seen with the combination of resveratrol and quercetin, and with resveratrol and pterostilbene.<sup>11</sup>

### Anti-Aging

David Sinclair and his research group first studied resveratrol's effect on yeast (*Saccharomyces cerevisiae*), fruit fly (*Drosophila melanogaster*), and roundworm (*Caenorhabditis elegans*). They found resveratrol increased the lifespan of these species by increasing the genetic expression of the SIR2 enzyme, a nicotinamide adenine dinucleotide (NAD)-dependent, sirtuin class of deacetylase. This enhancement of lifespan mimicked the known longevity-enhancing effect of caloric restriction.<sup>12</sup> In 2006 Sinclair's group published the seminal paper on resveratrol's effects on health and survival in mice.<sup>13</sup> Mice were fed a standard diet or a high-calorie diet with or without resveratrol. Both of the high-calorie diet groups gained weight; however, the resveratrol-fed group expressed increased insulin sensitivity, less fat deposition in the liver, an increased number of mitochondria per cell, and improved motor function. Another research group<sup>14</sup> supplemented mice with resveratrol at a much higher dose (20x) and found similar results, except the mice in the resveratrol group avoided the development of obesity and were able to run twice as far as the control group without fatigue. In mice, as in humans, the SIRT1 enzyme (the higher-mammal analog of SIR2) is up-regulated by resveratrol. Researchers postulated that up-regulation of SIRT1 could have been the reason for these physiological improvements in mice.<sup>13,14</sup> SIRT1 is a NAD-dependent enzyme that deacetylates a variety of target molecules, including peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1- $\alpha$ ), forkhead box O (FOX-01), and endothelial nitric oxide synthase (eNOS), which help regulate fat metabolism, gluconeogenesis and glycolysis in the liver, vascular health, and cell survival.<sup>15</sup>

Another possible mechanism of resveratrol's anti-aging effects might be induction of 5'AMP-activated protein kinase (AMPK). AMPK is important in fat metabolism in the liver, as it enhances fatty acid oxidation and down-regulates activity of HMG-CoA reductase, the rate-limiting step in cholesterol synthesis. In a study in which mice were fed a high-fat diet or a high-fat diet and resveratrol, wild-type mice fed resveratrol had an increase in metabolic rate, physical endurance, and

the number of mitochondria; however, in mice bred to lack AMPK, these metabolic effects were not seen.<sup>16</sup> Resveratrol has also been shown to enhance epinephrine-induced lipolysis and inhibit glucose conversion to lipids in rat adipocytes.<sup>17</sup>

### Anti-Inflammatory

Resveratrol expresses anti-inflammatory activity, which appears to be mediated by an inhibition of the activation of transcription factor nuclear factor-kappaB (NF- $\kappa$ B). Resveratrol inhibits NF- $\kappa$ B signaling, which in turn decreases transcription of DNA, and down-regulates inflammatory cytokine expression. Tumor necrosis factor-alpha (TNF- $\alpha$ ) treatment of adipocytes triggered increased NF- $\kappa$ B activation, resulting in increased interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2) gene expression; both resveratrol and the dietary polyphenol curcumin inhibited NF- $\kappa$ B activation, IL-6, and COX-2 expression.<sup>18</sup> Pearson et al found resveratrol treatment of mice had decreased expression of the inflammatory markers TNF- $\alpha$ , IL-6, IL-1 $\beta$ , intercellular adhesion molecule-1 (ICAM-1), and inducible nitric oxide synthase (iNOS).<sup>19</sup> In a mouse model of chronic colitis, resveratrol treatment resulted in significant decreases in the inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , as well as COX-2 and iNOS activity and an increase in the anti-inflammatory, immune-regulatory cytokine, IL-10.<sup>20</sup>

### Immune Regulation

In lipopolysaccharide-activated macrophages, resveratrol significantly inhibited the secretion of interferon-gamma (IFN- $\gamma$ ), IL-1, IL-4, IL-6, and TNF- $\alpha$ , while production of IL-10 was significantly increased. Immune-regulatory cells CD28 and CD80 were significantly down-regulated as well. The overall response was a down-regulation of both T-helper-1 and T-helper-2-directed immune activity. Curcumin exerted a similar response.<sup>21</sup>

### Vascular Support

C-reactive protein (CRP) is a non-specific inflammatory marker that is increased in acute and chronic inflammation and is a confirmed clinical marker of cardiovascular risk. Increased CRP can induce vascular endothelial dysfunction and promote atherosclerosis. Hep3B cells treated with IL-6 and IL-1 $\beta$  showed increased expression of CRP, which was inhibited by resveratrol or quercetin.<sup>22</sup> Resveratrol has also been shown to increase the activity of eNOS, which converts dietary L-arginine into nitric oxide in blood vessels.<sup>23,24</sup> Nitric oxide promotes vascular health by stimulating

vasodilation and inhibiting monocyte adhesion and vascular smooth muscle proliferation.

### Antineoplastic Activity

The development of cancer is a long-term process that can take decades to manifest clinically and can involve multiple cellular signaling pathways. Resveratrol has been studied for its effects on numerous cancer cell types and appears to exert its effects via many cellular mechanisms. One mechanism is via induction of an S-phase delay in cellular replication.<sup>25</sup> Researchers demonstrated a noncytotoxic inhibition of cell cycle activity in the S-phase of HepG2 cells with low-dose resveratrol (12.5 and 25  $\mu$ M), which was not seen with higher doses (50 and 100  $\mu$ M). At the higher doses, resveratrol induced apoptosis in HepG2 cells. Resveratrol also stimulated a non-apoptotic decrease in cell viability in HepG2 cells, as well as MCF-7 and MDA-MB435s breast cancer cells.

Resveratrol blocked TNF- $\alpha$ -induced activation of NF- $\kappa$ B and activator protein-1 (AP-1), possibly via inhibition of reactive oxygen species (ROS) and lipid peroxidation, as well as decreased phosphorylation and nuclear translocation of the p65 subunit of NF- $\kappa$ B. This is an important finding, as NF- $\kappa$ B regulates genes involved in inflammation, tumorigenesis, and metastasis. It is also significant because a concentration of 5  $\mu$ M was used, which is a relatively low dose and one achievable in the human body via red wine or grape consumption, or via supplementation.<sup>26</sup> A similar effect of resveratrol on NF- $\kappa$ B was seen in prostate cancer cells.<sup>27</sup>

Cyclooxygenase-2 is abundantly expressed in a variety of cancers and is a potential target for cancer prevention, as COX-2 activity produces inflammatory prostaglandins. Zykova et al found that resveratrol binds directly to COX-2 and inhibits its activity, in addition to inhibiting growth of HT-29 colon cancer cells.<sup>28</sup> Prostate cancer cells treated with either resveratrol or curcumin showed inhibition of TNF- $\alpha$  and IL-1 $\beta$ -induced expression of NF- $\kappa$ B activity and COX-2.<sup>29</sup>

Resveratrol was also found to act as a phytoestrogen that interacts with estrogen receptors on breast cancer cells. In breast cancer cells a number of mechanisms appear to be in play. Resveratrol increased expression of BRCA1 and BRCA2 in breast cancer cell lines; however, no change was noted in protein production induced by these genes.<sup>30</sup> In MCF-7 breast tumor cells, resveratrol induced apoptosis by interfering with the estrogen receptor-dependent phosphoinositide 3-kinase (PI3K) pathway. PI3K appears to regulate calpain,

which inhibits NF- $\kappa$ B nuclear translocation and promotes apoptosis.<sup>31</sup> Resveratrol appears to be a weak stimulator of MCF-7 cell growth, in a less potent fashion than estrogen. When resveratrol was introduced into cell cultures along with estrogen, resveratrol “antagonized the growth-stimulatory effect of E<sub>2</sub> in a dose-dependent fashion...,” and stimulated the growth-inhibitory transforming growth factor beta2 (TGF- $\beta$ 2).<sup>32</sup>

Filomeni et al found that incubation of MCF-7 breast cancer cells with resveratrol resulted in apoptosis caused by ROS and glutathione depletion. This finding shows resveratrol can alter cellular redox by exhibiting an antioxidant effect in normal cells and a pro-oxidant effect in cancer cells.<sup>33</sup> Other studies suggest inhibition of aromatase<sup>34</sup> and angiogenesis<sup>35</sup> by resveratrol in breast cancer. Resveratrol demonstrated antiangiogenic activity via inhibition of vascular endothelial growth factor (VEGF), metalloproteinases, and other mechanisms in multiple myeloma cells.<sup>36</sup>

### Clinical Indications

Almost all of the research on resveratrol to date has been *in vitro* or in animals, which makes it difficult to specifically indicate which clinical conditions will respond to resveratrol supplementation in humans. Most of the clinical indications below are extrapolated from the voluminous published nonclinical data.

#### Aging

Sinclair and others’ work in animals suggests resveratrol can combat oxidative stress, inflammation, insulin resistance, and might prolong life by mimicking the effects of caloric restriction.<sup>12,13,19,37,38</sup>

#### Cardiovascular Disease

Vascular nitric oxide synthesis is a vital component to vascular health. Nitric oxide promotes vasodilation, decreases leukocyte adhesiveness to vascular endothelial cells, acts as an antioxidant and anti-inflammatory, inhibits platelet aggregation, and inhibits smooth muscle proliferation – all health-promoting actions that help inhibit the atherosclerotic process and increase blood flow. Resveratrol stimulates the activity of eNOS, the enzyme involved in converting dietary or supplemental L-arginine to nitric oxide.<sup>23,39</sup> A human study on resveratrol’s effect on platelet aggregation found a significant inhibition of platelet aggregation *ex vivo* in a dose-dependent manner.<sup>40</sup>

Metabolism of the amino acid methionine creates homocysteine, which must be either remethylated to form methionine again or trans-sulfurated to form cysteine and taurine. Hyperhomocysteinemia is an independent risk factor for the development of cardiovascular disease. Homocysteine damages the vascular endothelium directly via oxidative stress and indirectly by other mechanisms, including induction of vascular cell adhesion molecule-1 (VCAM-1), which stimulates leukocytes to attach to the vascular endothelium, a pivotal step in the formation of atherosclerotic plaques. NF- $\kappa$ B stimulates the expression of VCAM-1; however, resveratrol was found to inhibit NF- $\kappa$ B-induced VCAM-1 expression.<sup>41</sup> Resveratrol was also found to inhibit TNF- $\alpha$  stimulation of VCAM-1 expression and neutrophil adhesion to endothelial cells.<sup>42</sup>

## Cancer

Of all the research on resveratrol, cancer is the topic that has been the most researched to date. Resveratrol has been extensively studied in breast and prostate cancers. Resveratrol exerts anti-cancer activity via numerous mechanisms, including its phytoestrogen effect, upregulation of SIRT1, inhibition of TNF- $\alpha$ -induced NF- $\kappa$ B activity, inhibition of COX-2, antioxidant activity, stimulation of apoptosis, and decreased angiogenesis and metastasis. An animal study of resveratrol's effect on colon cancer found resveratrol feeding reduced colon cancer incidence in mice induced by azoxymethane by 75 percent, indicating resveratrol may show promise for prevention or treatment of colon cancer.<sup>43</sup>

Osteosarcoma is a difficult cancer to treat due to a variety of cellular and metabolic aberrations that cause this type of cancer to demonstrate variable responses to conventional cancer therapeutics, including multiple drug resistance. Resveratrol consistently induced apoptosis in four osteosarcoma cell lines, but had little effect on normal cells, suggesting that resveratrol might be of benefit in this cancer type.<sup>44</sup>

Resveratrol introduced into ovarian cancer cells along with indole-3-carbinol caused cell cycle arrest, detachment, and apoptosis, demonstrating a synergistic effect of these two naturally-occurring, chemopreventive substances.<sup>45</sup>

A combination of resveratrol with quercetin and catechin, all polyphenols found in red wine, was used in a mouse breast cancer model, and resulted in cell cycle arrest and a significant decrease in cell proliferation. Interestingly, each of the

components given separately did not result in these inhibitory effects.<sup>46</sup>

## Cerebral Insufficiency

Cerebral blood flow is an important component of cognitive function, with a corresponding reduction in cognitive function with reduced cerebral perfusion.<sup>47</sup> In a randomized, placebo-controlled, double-blind study, 22 healthy adults were supplemented with 250 or 500 mg of trans-resveratrol or placebo. Forty-five minutes after taking the oral dose, cognitive tasks were performed and brain perfusion was measured. A dose-dependent increase in cerebral blood flow was demonstrated, without significant changes in cognitive function. Increased activity of eNOS with up-regulation of nitric oxide-dependent vasodilation was postulated as the mechanism for the increased blood flow.<sup>48</sup>

## Inflammatory Conditions

Numerous studies of resveratrol's anti-inflammatory activity suggest it is a potent anti-inflammatory that could be used in many clinical situations in which inflammation is involved. One such disease process is asthma; the primary allopathic treatment of asthma is the use of steroidal anti-inflammatory drugs to treat the chronic lung inflammation. In a study of inflammatory cytokine production in lung epithelial cells, resveratrol inhibited NF- $\kappa$ B expression, IL-8 release, iNOS, and COX-2 expression.<sup>49</sup> Another cell culture study revealed similar effects, with resveratrol inhibiting cytokine release from alveolar macrophages of patients with chronic obstructive pulmonary disease: resveratrol inhibited IL-8 release by 51 percent.<sup>50</sup> Arthritis is a poorly treated disease by Western medicine, with the over-the-counter and prescription drugs typically used having significant toxicity and side effects. Resveratrol's inhibitory effects on the downstream metabolites of NF- $\kappa$ B in human articular chondrocytes suggest it may be of benefit in arthritis.<sup>51,52</sup>

## Metabolic Syndrome/Type 2 Diabetes

Resveratrol supplementation in studies of mice fed high-fat diets demonstrated an inhibition of fat deposition in abdominal organs and an increase in insulin sensitivity, compared to control mice.<sup>13</sup> In streptozotocin-induced diabetes in rats, resveratrol supplementation had a significant effect of lowering blood glucose and triglycerides, which are commonly deranged in metabolic syndrome. Hepatic glycogen synthesis, as well as glucose

uptake in a variety of tissues, was stimulated by resveratrol, demonstrating a significant improvement in insulin sensitivity.<sup>53</sup> Resveratrol supplementation has also been shown to be protective of vascular endothelial cells in diabetes<sup>54</sup> and inhibits the typical inflammatory activity in experimental diabetic neuropathy<sup>55</sup> and nephropathy.<sup>56</sup> Resveratrol and curcumin together inhibited NF- $\kappa$ B-mediated inflammatory cytokines in adipocytes that perpetuate and worsen the metabolic syndrome.<sup>18</sup>

### Nonalcoholic- and Alcohol-Induced Fatty Liver

It is estimated that 25-percent of the American population has nonalcoholic fatty liver disease (NAFLD), which is a hallmark of obesity and metabolic syndrome and can lead to nonalcoholic steatohepatitis (NASH) and cirrhosis.<sup>57</sup> An animal study demonstrated resveratrol inhibited the development of fatty liver in rats fed a high-carbohydrate diet and subjected to periodic fasting. Resveratrol also inhibited oxidative stress and TNF- $\alpha$  levels.<sup>58</sup> A mouse model of alcoholic fatty liver disease also showed a preventive effect of resveratrol, with reduced lipid synthesis and increased fatty acid oxidation via up-regulation of SIRT1.<sup>59,60</sup>

### Side Effects and Toxicity

In a short-term, repeated-dose study, no serious adverse events were experienced; however, three individuals (12.5% of participants) experienced frontal headache. No biochemical, neurological, electrocardiographical, or other objective adverse effects were noted.<sup>7</sup>

### Drug-Nutrient Interactions

Resveratrol appears to inhibit cellular proliferation via an S-phase inhibition of the cell cycle. Two studies have shown a synergistic apoptotic effect of resveratrol and paclitaxel. Resveratrol introduced prior to paclitaxel to lung cancer cells caused a significant increase in cell death.<sup>61</sup> A similar sensitizing effect was seen in non-Hodgkin's lymphoma and multiple myeloma cells.<sup>62</sup> Other studies have demonstrated interference between resveratrol and paclitaxel, probably because of resveratrol's effect on the cell cycle. It is thought that resveratrol prevents tumor cells from progressing to the S1 phase, where paclitaxel exerts its apoptotic effect. Resveratrol reduced the antitumor efficacy of paclitaxel and vinblastine in bladder cancer cells; however, resveratrol pretreatment enhanced the cell-killing activity of these chemotherapeutic agents.<sup>63,64</sup>

Cisplatin and doxorubicin are commonly used chemotherapeutic drugs with well-known toxicity to the heart and kidneys. Resveratrol increased the effectiveness of these drugs and reduced doxorubicin toxicity in rat heart cells.<sup>65</sup> In another study, resveratrol pretreatment reduced the renal toxicity of cisplatin in rats.<sup>66</sup>

### Dosage

It has been postulated that a blood concentration of at least 5  $\mu$ mol/L is necessary for resveratrol's chemopreventive effects to be seen *in vitro*;<sup>6,67</sup> however, this does not rule out that resveratrol's sulfate and glucuronide metabolites have cancer chemopreventive properties of their own, as this has not been studied. Also, it might be possible that the blood levels of trans-resveratrol necessary for chemoprevention *in vivo* are lower than the levels needed for *in vitro* activity.

A daily dosage of 200-400 mg of trans-resveratrol may be of benefit in inflammatory diseases, metabolic syndrome and type 2 diabetes, anti-aging, and cardiovascular disease. Higher doses may be needed for cancer chemoprevention. Taking resveratrol along with synergistic polyphenols, such as curcumin, quercetin, and pterostilbene, may be helpful and require lower doses. Also, taking resveratrol with quercetin appears to slow the metabolism of resveratrol.<sup>3,5</sup>

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