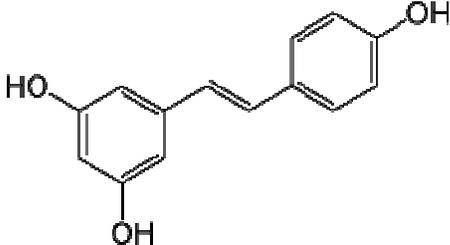
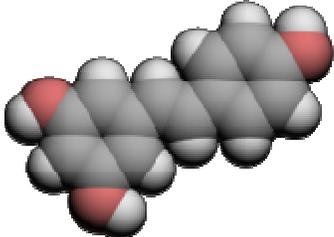


Resveratrol - Wikipedia

Resveratrol	
	
	
Other names	<i>trans</i> -3,5,4'-Trihydroxystilbene; 3,4',5-Stilbenetriol; <i>trans</i> -Resveratrol; (<i>E</i>)-5-(<i>p</i> -Hydroxystyryl)resorcinol (<i>E</i>)-5-(4-hydroxystyryl)benzene-1,3-diol
Properties	
Molecular formula	C ₁₄ H ₁₂ O ₃
Molar mass	228.25
Appearance	white powder with slight yellow cast
Solubility in water	0.03 g/L
Solubility in DMSO	16 g/L
Solubility in ethanol	50 g/L
Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa) Infobox references	

Resveratrol (*trans*-resveratrol) is a [phytoalexin](#) produced naturally by several plants when under attack by [pathogens](#) such as [bacteria](#) or [fungi](#). Resveratrol has also been produced by chemical synthesis^[1] and is sold as a [nutritional supplement](#) derived primarily from [Japanese knotweed](#). In mouse and rat experiments, anti-cancer, [anti-inflammatory](#), blood-sugar-lowering and other beneficial cardiovascular effects of resveratrol have been reported. Most of these results have yet to be replicated in humans. In the only positive human trial, extremely high doses (3–5 g) of resveratrol in a proprietary formulation have been necessary to significantly lower blood sugar.^[2] Resveratrol is found in the skin of red grapes and is a constituent of red wine, but apparently not in

sufficient amounts to explain the [French paradox](#). Experiments have shown that resveratrol treatment extended the life of fruit flies, nematode worms and short living fish but it did not increase the life span of mice.

Life extension

The groups of Howitz and Sinclair reported in 2003 in the journal [Nature](#) that resveratrol significantly extends the lifespan of the [yeast *Saccharomyces cerevisiae*](#).^[3] Later studies conducted by Sinclair showed that resveratrol also prolongs the lifespan of the worm [Caenorhabditis elegans](#) and the fruit fly [Drosophila melanogaster](#).^[4] In 2007, a different group of researchers was able to reproduce Sinclair's results with *C. elegans*,^[5] but a third group could not achieve consistent increases in lifespan of *D. melanogaster* or *C. elegans*.^[6]

In 2006, Italian scientists obtained the first positive result of resveratrol supplementation in a [vertebrate](#). Using a short-lived fish, [Nothobranchius furzeri](#), with a median life span of nine weeks, they found that a maximal dose of resveratrol increased the median lifespan by 56%. Compared with <http://en.wikipedia.org/wiki/Resveratrol> the control fish at nine weeks, that is by the end of the latter's life, the fish supplemented with resveratrol showed significantly higher general swimming activity and better learning to avoid an unpleasant stimulus. The authors noted a slight increase of mortality in young fish caused by resveratrol and hypothesized that it is its weak toxic action that stimulated the defense mechanisms and resulted in the life span extension.^[7]

Later the same year, Sinclair reported that resveratrol counteracted the detrimental effects of a high-fat diet in mice. The high fat diet was compounded by adding hydrogenated [coconut oil](#) to the standard diet; it provided 60% of energy from fat, and the mice on it consumed about 30% more calories than the mice on standard diet. Both the mice fed the standard diet and the high-fat diet plus 22 mg/kg resveratrol had a 30% lower risk of death than the mice on the high-fat diet. [Gene expression](#) analysis indicated the addition of resveratrol opposed the alteration of 144 out of 155 gene pathways changed by the high-fat diet. [Insulin](#) and [glucose](#) levels in mice on the high-fat+resveratrol diet were closer to the mice on standard diet than to the mice on the high-fat diet. However, addition of resveratrol to the high-fat diet did not change the levels of free fatty acids and cholesterol, which were much higher than in the mice on standard diet.^[8] A further study by a group of scientists, which included Sinclair, indicated that resveratrol treatment had a range of beneficial effects in elderly mice but did not increase the longevity of [ad libitum](#)-fed mice when started midlife.^[9]

Cancer prevention

In 1997, Jang reported that topical resveratrol applications prevented the skin cancer development in mice treated with a [carcinogen](#).^[10] There have since been dozens of studies of the anti-cancer activity of resveratrol in animal models.^[11] No results of human clinical trials for cancer have been reported.^[12] However, clinical trials to investigate the effects on colon cancer and [melanoma](#) (skin cancer) are currently recruiting patients.^[13]

[In vitro](#) resveratrol interacts with multiple molecular targets (see [the mechanisms of action](#)), and has positive effects on the cells of breast, skin, gastric, colon, esophageal, prostate, and pancreatic cancer, and leukemia.^[11] However, the study of pharmacokinetics of resveratrol in humans concluded that even high doses of resveratrol might be insufficient to achieve resveratrol concentrations required for the systemic prevention of cancer.^[14] This is consistent with the results from the animal cancer models, which indicate that the [in vivo](#) effectiveness of resveratrol is limited by its poor systemic bioavailability.^{[12][15][16]} The strongest evidence of anti-cancer action of resveratrol exists for tumors it can come into direct contact with, such as skin and [gastrointestinal tract](#) tumors. For other cancers, the evidence is equivocal, even if massive doses of resveratrol are used.^[12]

Thus, topical application of resveratrol in mice, both before and after the UVB exposure, inhibited the skin damage and decreased skin cancer incidence. However, oral resveratrol was ineffective in treating mice [inoculated](#) with melanoma cells. Resveratrol given orally also had no effect on leukemia and lung cancer;^{[12][17]} however, injected intraperitoneally, 2.5 or 10 mg/kg of resveratrol slowed the growth of metastatic Lewis lung carcinomas in mice.^{[12][18]} Resveratrol (1 mg/kg orally) reduced the number and size of the esophageal tumors in rats treated with a carcinogen.^[19] In several studies, small doses (0.02–8 mg/kg) of resveratrol, given prophylactically, reduced or prevented the development of intestinal and colon tumors in rats given different carcinogens.^[12]

Resveratrol treatment appeared to prevent the development of mammary tumors in animal models; however, it had no effect on the growth of existing tumors. Paradoxically, treatment of pre-pubertal mice with high doses of resveratrol enhanced formation of tumors. Injected in high doses into mice, resveratrol slowed the growth of [neuroblastomas](#).^[12]

Athletic performance

Johan Auwerx (at the Institute of Genetics and Molecular and Cell Biology in Illkirch, France) and coauthors published an online article in the journal [Cell](#) in November, 2006. Mice fed resveratrol for fifteen weeks had better treadmill endurance than controls. The study supported Sinclair's hypothesis that the effects of resveratrol are indeed due to the activation of the [Sirtuin 1](#) gene.

Nicholas Wade's interview-article with Dr. Auwerx^[20] states that the dose was 400 mg/kg of body weight (much higher than the 22 mg/kg of the Sinclair study). For an 80 kg (176 lb) person, the 400 mg/kg of body weight amount used in Auwerx's mouse study would come to 32,000 mg/day. Compensating for the fact that humans have slower metabolic rates than mice would change the equivalent human dose to roughly 4571 mg/day. Again, there is no published evidence anywhere in the scientific literature of any clinical trial for efficacy in humans. There is limited human safety data (see above). Long-term safety has not been evaluated in humans.

In a study of 123 Finnish adults, those born with certain increased variations of the SIRT1 gene had faster metabolisms, helping them to burn energy more efficiently—indicating that the same pathway shown in the lab mice works in humans.^[21]

Neurodegenerative disease

In November 2008, researchers at the Weill Medical College of Cornell University reported that dietary supplementation with resveratrol significantly reduced plaque formation in animal brains, a component of [Alzheimer](#) and other Neurodegenerative diseases.^[22] In mice, oral resveratrol produced large reductions in brain plaque in the hypothalamus (-90%), striatum (-89%), and medial cortex (-48%) sections of the brain. In humans it is theorized that oral doses of resveratrol may reduce beta amyloid plaque associated with aging changes in the brain. Researchers theorize that one mechanism for plaque eradication is the ability of resveratrol to chelate (remove) copper.

Radiation protection

In September 2008, a study by the University of Pittsburgh School of Medicine found that resveratrol may offer protection against radiation exposure.^[23]

Pharmacokinetics

The most efficient way of administering resveratrol in humans appears to be [buccal](#) delivery, that is without swallowing, by direct absorption through the inside of the mouth. When one mg of resveratrol in 50 mL solution was retained in the mouth for one min before swallowing, 37 ng/ml of free resveratrol were measured in plasma two minutes later. This level of unchanged resveratrol in blood can only be achieved with 250 mg of resveratrol taken in a pill form.^[24]

About 70% of the resveratrol dose given orally as a pill is absorbed; nevertheless, oral [bioavailability](#) of resveratrol is low because it is rapidly metabolized in intestines and liver into [conjugated](#) forms: [glucuronate](#) and [sulfonate](#).^[25] Only trace amounts (below 5 ng/mL) of unchanged resveratrol could be detected in the blood after 25 mg oral dose.^[25] Even when a very large dose of resveratrol (2.5 and 5 g) was given as an uncoated pill, the concentration of resveratrol in blood failed to reach the level necessary for the systemic cancer prevention.^[26] However, resveratrol given in a proprietary formulation SRT-501 (3 or 5 g), developed by Sirtris Pharmaceuticals, reached 5-8 times higher blood levels. These levels did approach the concentration necessary to exert the effects shown in animal models and in vitro experiments.^[2]

In humans^{[25][26]} and rats,^{[27][28][29]} less than 5% of the oral dose is being observed as free resveratrol in blood plasma. The most abundant resveratrol metabolites in humans, rats, and mice are trans-resveratrol-3-O-glucuronide and trans-resveratrol-3-sulfate.^[30] Walle suggests sulfate conjugates are the primary source of activity^[25], Wang et al. suggests the glucuronides,^[31] and Boocock et al. also emphasized the need for further study of the effects of the [metabolites](#), including the possibility of deconjugation to free resveratrol inside cells. Goldberd, who studied the [pharmacokinetics](#) of resveratrol, [catechin](#) and [quercetin](#) in humans, concluded "it seems that the potential health benefits of these compounds based upon the in vitro activities of the unconjugated compounds are unrealistic and have been greatly exaggerated. Indeed, the profusion of papers describing such activities can legitimately be described as irrelevant and misleading. Henceforth, investigations of this nature should focus upon the potential health benefits of their [glucuronide](#) and [sulfate](#) conjugates."^[32]

The hypothesis that resveratrol from wine could have higher [bioavailability](#) than resveratrol from a pill,^{[11][33]} has been disproved by experimental data.^{[32][34]} For example, after five men took 600 mL of red wine with the resveratrol content of 3.2 mg/L (total dose about 2 mg) before breakfast, unchanged resveratrol was detected in the blood of only two of them, and only in trace amounts (below 2.5 ng/mL). Resveratrol levels appeared to be slightly higher if red wine (600 mL of red wine containing 0.6 mg/mL resveratrol; total dose about 0.5 mg) was

taken with meal: trace amounts (1–6 ng/mL) were found in four out of ten subjects.^[34] In another study, the pharmacokinetics of resveratrol (25 mg) did not change whether it was taken with vegetable juice, white wine or white grape juice. The highest level of unchanged resveratrol in the [serum](#) (7-9 ng/mL) was achieved after thirty minutes, and it completely disappeared from blood after four hours.^[32] The authors of both studies concluded that the trace amounts of resveratrol reached in the blood are insufficient to explain the French paradox. It appears that the beneficial effects of wine could be explained by the effects of alcohol^[32] or the whole complex of substances wine contains^[34]; for example, the cardiovascular benefits of wine appear to correlate with the content of [procyanidins](#).^[35]

Adverse effects and unknowns

While the health benefits of resveratrol seem promising, one study has theorized that it may stimulate the growth of human [breast cancer](#) cells, possibly because of resveratrol's chemical structure, which is similar to a [phytoestrogen](#).^{[36][37]} However, other studies have found that resveratrol actually fights breast cancer.^{[38][39]} Some studies suggest that resveratrol slows the development of blood vessels, which suppresses tumors, but also slows healing.^[40] Citing the evidence that resveratrol is [estrogenic](#), some retailers of resveratrol advise that the compound may interfere with oral contraceptives and that women who are pregnant or intending to become pregnant should not use the product, while others advise that resveratrol should not be taken by children or young adults under eighteen, as no studies have shown how it affects their natural development.^[41] A small study found that a single dose of up to 5 g of *trans*-resveratrol caused no serious adverse effects in healthy volunteers.^[14]

Mechanisms of action

The mechanisms of resveratrol's apparent effects on [life extension](#) are not fully understood, but they appear to mimic several of the [biochemical](#) effects of [calorie restriction](#). A new report indicates that resveratrol activates [Sirtuin 1](#) (SIRT1) and PGC-1 α and improve functioning of the [mitochondria](#).^[42] Other research calls into question the theory connecting resveratrol, SIRT1, and calorie restriction.^{[43][44]}

For the debate about Resveratrol effects on longevity, see [Calorie restriction#Sir2.2/SIRT1 and resveratrol](#).

A paper by Robb *et al.* discusses resveratrol action in cells. It reports a fourteen-fold increase in the action of MnSOD ([SOD2](#)).^[45] MnSOD reduces superoxide to [hydrogen peroxide](#) (H₂O₂), but H₂O₂ is not increased due to other cellular activity. Superoxide O₂⁻ is a byproduct of respiration in complex 1 and 3 of the [electron transport chain](#). It is "not highly toxic, [but] can extract an electron from biological membrane and other cell components, causing free radical chain reactions. Therefore it is essential for the cell to keep superoxide anions in check."^[46] MnSOD reduces superoxide and thereby confers resistance to [mitochondrial dysfunction](#), permeability transition, and [apoptotic](#) death in various diseases.^[47] It has been implicated in lifespan extension, inhibits cancer, (e.g. pancreatic cancer^{[48][49]}) and provides resistance to reperfusion injury and irradiation damage^{[50][51][52]}. These effects have also been observed with resveratrol. Robb et al. propose MnSOD is increased by the pathway RESV → SIRT1 / NAD⁺ → FOXO3a → MnSOD. Resveratrol has been shown to cause SIRT1 to cause migration of FOXO transcription factors to the nucleus^[53] which stimulates FOXO3a transcriptional activity^[54] and it has been shown to enhance the sirtuin-catalyzed deacetylation (activity) of [FOXO3a](#). MnSOD is known to be a target of FOXO3a, and MnSOD expression is strongly induced in cells overexpressing FOXO3a^[55].

Resveratrol interferes with all three stages of [carcinogenesis](#) — initiation, promotion and progression. Experiments in [cell cultures](#) of varied types and isolated subcellular systems [in vitro](#) imply many mechanisms in the [pharmacological](#) activity of resveratrol. These mechanisms include modulation of the [transcription factor NF- \$\kappa\$ B](#),^[56] inhibition of the [cytochrome P450](#) isoenzyme [CYP1A1](#)^[57] (although this may not be relevant to the CYP1A1-mediated bioactivation of the procarcinogen [benzo\(a\)pyrene](#)^[58]), alterations in [androgenic](#)^[59] actions and expression and activity of [cyclooxygenase](#) (COX) enzymes. In vitro, resveratrol "inhibited the proliferation of human pancreatic cancer cell lines." In some lineages of cancer [cell culture](#), resveratrol has been shown to induce [apoptosis](#), which means it kills cells and may kill cancer cells.^{[59][60][61][62][63][64]} Resveratrol has been shown to induce Fas/Fas [ligand](#) mediated [apoptosis](#), [p53](#) and [cyclins](#) A, B1 and [cyclin-dependent kinases](#) cdk 1 and 2. Resveratrol also possesses [antioxidant](#) and anti-[angiogenic](#) properties.^{[65][66]}

Resveratrol was reported effective against [neuronal](#) cell dysfunction and cell death, and in theory could help against diseases such as [Huntington's disease](#) and [Alzheimer's disease](#).^{[67][68]} Again, this has not yet been tested in humans for any disease.

Research at the [Northeastern Ohio Universities College of Medicine](#) and [Ohio State University](#) indicates that resveratrol has direct inhibitory action on cardiac fibroblasts, and may inhibit the progression of [cardiac fibrosis](#).^[69]

According to [Patrick Arnold](#), it also [significantly](#) increases natural [testosterone](#) production from being both a [selective estrogen receptor modulator](#)^{[70][71]} and an [aromatase inhibitor](#).^{[72][73]}

In December 2007, work from Irfan Rahman's laboratory at the [University of Rochester](#) demonstrated that resveratrol increased intracellular glutathione levels via Nrf2-dependent upregulation of [gamma-glutamylcysteine](#) ligase in lung epithelial cells, which protected them against cigarette smoke extract induced oxidative stress.^[74]

Chemical and physical properties

Resveratrol (3,5,4'-trihydroxystilbene) is a [polyphenolic phytoalexin](#). It is a [stilbenoid](#), a derivative of [stilbene](#), and is produced in plants with the help of the enzyme stilbene synthase.

It exists as two [geometric isomers](#): *cis*- (*Z*) and *trans*- (*E*), with the *trans*-isomer shown in the top image. The *trans*- form can undergo isomerisation to the *cis*- form when exposed to [ultraviolet](#) irradiation.^[75] *Trans*-resveratrol in the powder form was found to be stable under "accelerated stability" conditions of 75% humidity and 40 degrees C in the presence of air.^[76] Resveratrol content also stayed stable in the skins of grapes and [pomace](#) taken after fermentation and stored for a long period.^[77]

Plants and foods

Resveratrol was originally isolated by Takaoka from the roots of [white hellebore](#) in 1940, and later, in 1963, from the roots of [Japanese knotweed](#). However, it attracted wider attention only in 1992, when its presence in wine was suggested as the explanation for cardioprotective effects of wine.^[11]

In grapes, resveratrol is found primarily in the skin,^[78] and — in muscadine grapes — also in the seeds.^[79] The amount found in grape skins also varies with the grape cultivar, its geographic origin, and exposure to fungal infection. The amount of fermentation time a wine spends in contact with grape skins is an important determinant of its resveratrol content.^[78]

The levels of resveratrol found in food varies greatly. Red wine contains between 0.2 and 5.8 mg/L,^[80] depending on the grape variety, while white wine has much less — the reason being that red wine is [fermented](#) with the skins, allowing the wine to absorb the resveratrol, whereas [white wine](#) is fermented after the skin has been removed.^[78] A number of reports have indicated that [muscadine](#) grapes may contain high concentrations of resveratrol and that wines produced from these grapes, both red and white, may contain more than 40 mg/L.^{[79][81]} However, subsequent studies have found little or no resveratrol in different varieties of muscadine grapes.^{[82][83]}

The fruit of the [mulberry](#) (esp. the skin^[84]) is a source, and sold as a nutritional supplement.

Content in wines and grape juice

Beverage	Total resveratrol (mg/L) ^{[78][79]}	Total resveratrol in 150 mL wine (mg) ^{[78][79]}
Red Wines (Global)	1.98 - 7.13	0.30 - 1.07
Red Wines (Spanish)	1.92 - 12.59	0.29 - 1.89
Red grape juice (Spanish)	1.14 - 8.69	0.17 - 1.30
Rose Wines (Spanish)	0.43 - 3.52	0.06 - 0.53
Pinot Noir	0.40 - 2.0	0.06 - 0.30
White Wines (Spanish)	0.05 - 1.80	0.01 - 0.27

The *trans*-resveratrol concentration in forty Tuscan wines ranged from 0.3 to 2.1 mg/L in the 32 red wines tested and had a maximum of 0.1 mg/L in the 8 white wines in the test. Both the *cis*- and *trans*-isomers of resveratrol were detected in all tested samples. *cis*-Resveratrol levels were comparable to those of the *trans*-isomer. They ranged from 0.5 mg/L to 1.9 mg/L in red wines and had a maximum of 0.2 mg/L in white wines.^[85]

In a review of published resveratrol concentrations, the average resveratrol concentration in red wines is 1.9 ± 1.7 mg trans-resveratrol/l (8.2 ± 7.5 μ M), ranging from non-detectable levels to 14.3 mg/l (62.7 μ M) trans-resveratrol. Levels of *cis*-resveratrol follow the same trend as trans-resveratrol.^[86]

Reports suggest that some aspect of the wine making process converts [piceid](#) to resveratrol in wine, as wine seems to have twice the average resveratrol concentration of the equivalent commercial juices.^[79]

In general, wines made from grapes of the Pinot Noir and St. Laurent varieties showed the highest level of trans-resveratrol, though no wine or region can yet be said to produce wines with significantly higher resveratrol concentrations than any other wine or region.^[86]

Content in selected foods

Food	Serving	Total resveratrol (mg) ^[87]
Peanuts (raw)	1 c (146 g)	0.01 - 0.26
Peanuts (boiled)	1 c (180 g)	0.32 - 1.28
Peanut butter	1 c (258 g)	0.04 - 0.13
Red grapes	1 c (160 g)	0.24 - 1.25

Ounce for ounce, peanuts have about half the amount of resveratrol as that found in red wine. The average amount of resveratrol in one ounce of peanuts in the marketplace (about 15 whole) is 79.4 µg/ounce.

In comparison, some red wines contain approximately 160 µg/fluid ounce.^[88] Resveratrol was detected in grape, cranberry, and wine samples. Concentrations ranged from 1.56 to 1042 nmol/g in Concord grape products, and from 8.63 to 24.84 micromol/L in Italian red wine. The concentrations of resveratrol were similar in cranberry and grape juice at 1.07 and 1.56 nmol/g, respectively.^[89]

[Blueberries](#) have about twice as much resveratrol as [bilberries](#), but there is great regional variation. These fruits have less than ten percent of the resveratrol of grapes. Cooking or heat processing of these berries will contribute to the degradation of resveratrol, reducing it by up to half.^[90]

Supplementation

Resveratrol [nutritional supplements](#), first sourced from ground dried grape skins and seeds, are now primarily derived from the less expensive, more concentrated [Japanese knotweed](#), which contains up to 187 mg/kg in the dried root and can be concentrated in an extract up to 50%.^[91]

As a result of extensive news coverage,^{[92][93]} sales of supplements greatly increased in 2006,^{[94][95]} despite cautions that benefits to humans are unproven.^{[95][96][97]}

See also



[Pharmacy and Pharmacology portal](#)

Other articles

- [Codex Alimentarius](#)
- [Japanese knotweed](#)
- [List of grape varieties](#)
- [Mulberry](#)
- [Muscadine](#)
- [Piceatannol](#), an active [metabolite](#) of resveratrol.
- [Proanthocyanidin](#)
- [Polyphenol antioxidant](#)

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Further reading

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