

CLINICAL AND MEDICINAL APPLICATIONS OF RESVERATROL: A REVIEW

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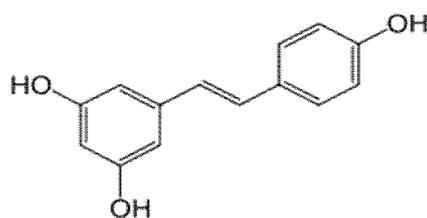
ABSTRACT

Resveratrol is a flavonol belonging to the group of flavonoids. It is produced by the plant as a defence against diseases. Resveratrol is present in many plants and fruits, including red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts, giant knotweed. Resveratrol is an antioxidant but its antioxidant properties are weaker than those of quercetin and epicatechin. It has anticancer properties and inhibits lipid peroxidation of low-density lipoprotein and prevents the cytotoxicity of oxidized LDL. Resveratrol also increases the activity of some antiretroviral drugs in vitro. Resveratrol protects our heart and blood vessels by directly scavenging oxidants, which could cause oxidation of lipids, and by preventing apoptosis of endothelial cells. It may also help to prevent heart damage after a cardiac arrest. Reduced platelet aggregation has been attributed to resveratrol, thereby reducing the risk of atherosclerosis. Tests with animals have shown that high food intake reduces lifespan. One study showed that resveratrol was able to increase the life span of mice on a high calorie diet. Many studies on animals have shown antioxidant effects of resveratrol. Resveratrol was able to reverse damages caused by the administration of the chemotherapeutic drug bleomycin. Resveratrol also helped to reduce brain damage and oxidative damage of the liver during ethanol intoxication. It also reduced kidney damage of rats treated with the antibiotic gentamicin. In the present article, we have concentrated on potential clinical and medicinal applications of Resveratrol. The aim of present article is to provide in depth knowledge about clinical utility of Resveratrol in current scenario.

Keywords: Resveratrol, trans-resveratrol, phytoalexin, 3, 4', 5-Stilbenetriol, trans-3, 5, 4'-Trihydroxystilbene.

INTRODUCTION

Resveratrol is a phytoalexin produced naturally by several plants when under attack by pathogens such as bacteria or fungi. Resveratrol is currently a topic of numerous animal and human studies into its effects. The effects of resveratrol on the lifespan of many model organisms remain controversial, with uncertain effects in fruit flies, nematode worms¹, and short-lived fish. 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 sugar². Despite mainstream press alleging resveratrol's anti-aging effects, there is little present scientific basis for the application of these claims to mammals. 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. Resveratrol has also been produced by chemical synthesis³ and is sold as a nutritional supplement derived primarily from Japanese knotweed.



Trans-resveratrol

RECENT STUDIES

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*⁴. Later studies conducted by Sinclair showed that resveratrol also prolongs the lifespan of the worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*⁵. In 2007, a different group of researchers were able to reproduce Sinclair's results with *Caenorhabditis elegans*⁶, but a third group could not achieve consistent increases in lifespan of *D. melanogaster* or *C. elegans*. 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 the control fish at nine weeks that is by the end of control fish'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 extension⁷.

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 153 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 diet⁸. 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 midlife⁹.

Cancer prevention

In 1997, Jang reported that topical resveratrol applications prevented skin cancer development in mice treated with a carcinogen¹⁰. There have since been dozens of studies of the anti-cancer activity of resveratrol in animal models¹¹. No results of human clinical trials for cancer have been reported¹². However, clinical trials to investigate the effects on colon cancer and melanoma (skin cancer) are currently recruiting patients.

In vitro resveratrol interacts with multiple molecular targets, and has positive effects on the cells of breast, skin, gastric, colon, esophageal, prostate, and pancreatic cancer, and leukemia. 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 cancer¹³. 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^{14, 15}. 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 uncertain, even if massive doses of resveratrol are used.

Thus, topical application of resveratrol in mice, both before and after the UVB (Ultraviolet B or medium wave) 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 cancer¹⁶; however, injected intraperitoneally, 2.5 or 10 mg/kg of resveratrol slowed the growth of metastatic Lewis lung carcinomas in mice¹⁷. Resveratrol (1 mg/kg orally) reduced the number and size of the esophageal tumors in rats treated with a carcinogen¹⁸. 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.

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.

Other applications

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. Auwerx¹⁹ 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. 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.

Neuroprotective effects

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 diseases²⁰. 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 (bind) copper. The neuroprotective effects have been confirmed in several animal model studies²¹⁻²⁵.

Anti-inflammatory effects

The anti-inflammatory effects of resveratrol have been demonstrated in several animal model studies. In a rat model of carrageenan-induced paw edema, resveratrol inhibited both acute and chronic phases of the inflammatory process²⁶. Similarly, preincubation with resveratrol decreased arachidonic acid release and COX-2 induction in mouse peritoneal macrophages stimulated with tumor promoter PMA, ROI, or lipopolysaccharides (LPS)²⁷. In an experimental rabbit inflammatory arthritis model, resveratrol has showed promise as a potential therapy for arthritis. When administered to rabbits with induced inflammatory arthritis, resveratrol protected cartilage against the progression of inflammatory arthritis²⁸.

Cardioprotective effects

It has long been known that moderate drinking of red wine reduces the risk of heart disease²⁹. Studies suggest that resveratrol in red wine may play an important role in this phenomenon³⁰. It achieves the effects by the following functions: (1) Inhibition of vascular cell adhesion molecule expression; (2) Inhibition of vascular smooth muscle cell proliferation; (3) Stimulation of endothelial nitric oxide synthase (eNOS) Activity; (4) Inhibition of platelet aggregation; (5) Inhibition of LDL peroxidation; The cardioprotective effects of resveratrol are also theorized to be a form of preconditioning—the best method of cardioprotection, rather than direct therapy³¹.

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*). The *trans*- form can undergo isomerisation to the *cis*- form when exposed to ultraviolet irradiation³². *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. Resveratrol content also stayed stable in the skins of grapes and pomace taken after fermentation and stored for a long period.

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