Review Article

Health Benefits of Resveratrol

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ABSTRACT: Resveratrol a polyphenolic phytoalexin possesses a variety of bioactivities associated with health promotion. Resveratrol is readily absorbed along with the other human dietary sources like peanuts, peanut butter, grapes, and red wine. The polyphenolic structure of resveratrol confers antioxidant activity and may reduce oxidant-induced apoptosis and low-density lipoprotein (LDL) oxidation. The cardioprotective activity of resveratrol is associated with the inhibition of platelet aggregation and LDL oxidation and the promotion of artery vasorelaxation. As a chemopreventing agent, resveratrol has been shown to inhibit tumor initiation, promotion, and progression, as well as inhibit the growth of cancerous cells through increased apoptosis and/or cell cycle blockage. Inflammatory processes are associated with the pathogenesis of many chronic diseases including heart disease and diabetes. In addition, the estrogenic activity of resveratrol may help in the prevention of post-menopausal osteoporosis. This review reveals potential health benefits and discusses the current preclinical studies of resveratrol.

KEYWORDS: Resveratrol, pharmacokinetics, Antioxidant, Breast cancer.

Introduction

One of the defence responses of plants to infection is the induced accumulation of antimicrobial, low-molecular-weight secondary metabolites known as phytoalexins (Fremont F, 2000). Resveratrol (3, 5, 4’-trihydroxy stilbene) is a polyphenolic phytoalexin produced naturally by several plants when attacked by bacteria and fungi. Phytoalexins are antibacterial and anti-fungal chemicals produced by plants for the defence against infections by pathogens. Resveratrol which is one of the potent antioxidant is present in red grapes, mulberries and in blue berries, bilberries (Philippe Marambaud et al., 2005), they are also present in other plants, such as eucalyptus, spruce, and lily, and in other foods such as peanuts. Resveratrol's most abundant natural sources are *Vitis vinifera*, labrusca, and muscadine grapes, *Polygonum cuspidatum* sieb.

Properties of resveratrol

Resveratrol is a stilbenoid, a derivative of stilbene, which is produced in plants with help of enzyme stilbene synthatase and it is a fat-soluble compound that exists in a trans-(E) and a cis-(Z) configuration. Both cis- and trans-resveratrol occur as glucosides (bound to a glucose molecule).

![Molecular structure of resveratrol](image)

Pharmacokinetics

In humans, resveratrol rapidly undergoes phase II conjugation, both glucuronidation and sulphonation at multiple sites on the molecule. The effect of conjugation on efficacy is debated (Goddard I, 2007). The pharmacokinetics of resveratrol metabolism has not been investigated in humans. In rats its half-life is 1.6 h. In 2002, Marier et. al., reported that rats given a single oral dose of 30 mg/kg body weight initially experienced a
rapid drop in serum resveratrol levels, the half life, or $t_{1/2}$, of the drug was found to be 8 minutes. However, detectable levels of the drug remained for 12 hours, probably due to enterohepatic recirculation. Resveratrol’s bioavailability depends on its conjugate forms, glucuronate and sulfonate, despite, most of the in vitro studies use the aglycone form of resveratrol. Resveratrol was quickly metabolized at 25 mg dose in humans. Only trace amounts were found in human plasma, and that most of the oral dose was recovered in urine. In mice, on the other hand, were found to have much larger amounts of resveratrol measured in their plasma using equivalent doses of resveratrol per kilogram of weight. It was also stated that the systemic bioavailability of resveratrol is very low in humans compared to mice, but that accumulation of resveratrol in the human epithelial cells along the digestive tract with potentially active resveratrol metabolites may still produce cancer-preventive and other effects. Large doses could theoretically increase the levels of resveratrol in human plasma.

**Various Potential Benefits of Resveratrol**

**Anticancer Effects**

Resveratrol was studied for its effects like the initiation, promotion, and progression of cancer (Gusman J, Yang CS et al., 2001; Jang M et al., 1997). Resveratrol a tiny molecule penetrates the cell membrane and nucleus in an organism. There, Resveratrol selectively switches on genes that aid the survival of an organism, like the Sirtuin 1 DNA-repair gene. Using gene silencing, it switches off genes involved in the initiation and progression of disease, blocking replication of tumor cells. Few proposed mechanisms of the antitumor effects of resveratrol includes activation of the expression of p53 (Yang HY, 2006). Fas-Fas ligand system, and mitogen-activated protein kinase (MAPK) signaling pathway, inhibition of p450 1A1, ribonucleotide reductase, ornithine decarboxylase, protein kinase C, DNA polymerase, cyclo-oxygenase, cell cycle progression and induces cellular apoptosis. With regard to tumor initiation, it has been shown to act as an antioxidant by inhibiting free radical formation and as an anti-mutagen in rat models. Resveratrol also inhibits the formation of 12-O-tetradecanoylphorbol-13-acetate (TPA). It is a cancer chemo preventive agent that reduces the incidence of tumorgenesis (Savouret, 2002) by intervening at one or more stages of carcinogenesis (Yang CS et al., 2001) thus acting as an anti-initiation agent. Further evidence indicated that resveratrol selectively suppresses the transcriptional activation of cytochrome p450 1A1 and inhibits the formation of carcinogen-induced preneoplastic lesions in a mouse mammary organ culture model, promoted mouse skin tumors in a two-stage model. Resveratrol appears to decrease tumor promotion by inhibiting cyclooxygenase-1 (COX-1), an enzyme that converts arachidonic acid to pro-inflammatory substances that stimulate tumor-cell growth. The enzymatic activities of COX-1 and -2 are inhibited by resveratrol in cell-free models, and COX-2 mRNA, TPA-induced activation of protein kinase C and AP-1-mediated gene expression are suppressed by resveratrol in mammary epithelial cells. In addition, resveratrol strongly inhibits nitric oxide synthase generation and inducible nitric oxide synthase protein expression. NF-κB is important for the regulation of cell proliferation, cell transformation, and tumor development (Baldwon AS, 1996; Ghosh S et al., 1996). NF-κB is strongly linked to inflammatory and immune responses and is associated with oncogenesis in certain models of cancer (Marier JF et al., 2002). Resveratrol suppresses the induction of this transcription factor by a number of mechanisms. The mechanism may involve decreasing the phosphorylation and degradation of IκBα, SR-IκBα, which cannot be phosphorylated or degraded, binds to NF-κB and blocks the nuclear translocation and subsequent transactivation of NF-κB-responsive genes. At the cellular level, Resveratrol also induces apoptosis, cell cycle delay or a block in the G1→S transition phase in a number of cell lines. Studies related to progression have found that resveratrol induced human promyelocytic leukemia cell differentiation and inhibited ribonucleotide reductase, an enzyme needed for DNA synthesis in proliferating cells. Resveratrol could suppress the proliferation of multiple myeloma (MM) cells by interfering with NF-κB and STAT3 pathways. Resveratrol inhibits the proliferation of human multiple myeloma cell lines which is mediated through suppression of constitutively active NF-κB through inhibition of IκBα kinase the phosphorylation of IκBα and of p65. Resveratrol inhibits both the constitutive and the interleukin 6–induced activation of STAT3. Thus resveratrol may have a potential in the treatment of multiple myeloma.

**Treatment of Lung Cancer by Resveratrol**

Resveratrol is reported to have protective effects against lung cancer. It involves in the up-regulation of p53 and p21 and the induction of apoptosis by the activation of the caspases and the disruption of the mitochondrial membrane complex. It shows the arrest of A549 cells in the G1 phase of cell cycle. Resveratrol action is mediated via the transforming growth factor-β pathway, particularly through the Smad proteins. Resveratrol is a potent inhibitor of A549 lung cancer.
Resveratrol Suppresses Breast Cancers
Resveratrol suppresses the abnormal cell formation that leads to various types of breast cancer, suggesting its potential role in breast cancer prevention (Krappmann D et al., 1999). The formation of breast cancer is a multi-step process which differs depending on type of disease, a patient's genetic makeup and other factors. However, scientists know that many breast cancers are fueled by increased estrogen, which collects and reacts with DNA molecules to form adducts. Resveratrol has the ability to prevent the first step that occurs when estrogen starts the process that leads to cancer by blocking the formation of the estrogen DNA adducts. Resveratrol induces an enzyme called quinone reductase, which reduces the estrogen metabolite back to inactive form. By making estrogen inactive, resveratrol decreases the associated risk. The researchers also found that resveratrol suppressed the expression of CYP1B1 and the formation of 2,3,7,8 tetrachloro dibenzo-p-dioxin, two known risk factors for breast cancer. Resveratrol increases cAMP but it had no effect on cGMP levels. The stimulatory effects for resveratrol on adenylate-cyclase augmented maximal cAMP formation. The chemotherapeutic agent resveratrol is an agonist for the cAMP/kinase-A system, a pro-apoptotic and cell-cycle suppressor in breast cancer cells. Resveratrol is a phytoestrogen that displays estrogen-like agonistic (Gehm BD, 1997) and antagonistic activity (Basly JP et al., 2000), which appears to mediate some of its actions by modulating the estrogen machinery and act as an anti-breast cancer agent (Gehm BD, 1997; Srivastava RK et al., 1998). Interestingly, products of adenylate-cyclase and guanylate-cyclase enzymes; namely cAMP and cGMP, can trigger both cytostatic and pro-apoptotic signals in breast cancer cells (Bani D, 1995 and Sovak MA et al., 1997).

Estrogenic Activity
Resveratrol was found to have both estrogenic/anti-estrogenic activities (Bowers JL et al., 2000). The similarity in structure between resveratrol and diethylstilbestrol (a synthetic estrogen) has prompted investigations into resveratrol's potential as a phytoestrogen (a plant compound that produces estrogen-like effects). However, these properties also stimulate the growth of human breast cancer cells. This finding seems contrary to its other anticancer activities, and is a cause for concern. Thus, resveratrol holds great promise for future development as a chemo preventive agent that may be useful for several disorders. Preclinical toxicity studies are underway that should be followed by human clinical trials. However, other studies have found that resveratrol actually fights breast cancer. Citing the evidence that resveratrol is estrogenic, some retailers of resveratrol advice that the compound may interfere with oral contraceptives and that women who are pregnant or intend to become pregnant should not use the product. Still there are no studies which show how it affects natural development; others advise that resveratrol should not be taken by children or young adults under 18.

Prevention of Cardiovascular Diseases
Recently the polyphenol resveratrol has been demonstrated to elicit a broad spectrum of biological responses in in vitro and in animal studies, including effects that are compatible with the cardio protective roles. Recent studies relating exposure to resveratrol with reduction in myocardial damage during ischemia-reperfusion, modulation of vascular cell functions, inhibition of LDL oxidation, and suppression of platelet aggregation has been presented. It inhibits lipid peroxidation of low-density lipoprotein (LDL), prevents the cytotoxicity of oxidized LDL, and protects cells against lipid peroxidation. It is thought that as it contains highly hydrophilic and lipophilic properties, it can provide more effective protection than other well-known antioxidants, such as vitamin C and vitamin E. Research also indicates that resveratrol has direct inhibitory action on cardiac fibroblasts and may inhibit the progression of cardiac fibrosis.

Anti-platelet Aggregation
The clumping of blood platelets causes blood clotting and thrombosis. Resveratrol is active in preventing platelets from bunching up together and it keeps the blood smoothly flowing through arteries. Recent studies report that resveratrol freely dilates blood vessels bringing down the blood pressure.

Hypoglycemic and Hypolipidemic Effects
Resveratrol is reported to possess hypoglycemic and hypolipidemic effects in streptozotocin-induced DM (STZ-DM) rats. Glucose uptake by hepatocytes, adipocytes, and skeletal muscle and hepatic glycogen synthesis were stimulated by resveratrol treatment. As the stimulation of glucose uptake was not attenuated in the presence of an optimal amount of insulin in insulin-responsive cells, the antihyperglycemic effect of resveratrol appeared to act through different mechanism(s) from that of insulin. In vitro, trans-resveratrol and rumexoid demonstrated a potent inhibitory effect on α-glucosidase activity. In addition, it inhibits production of cytokines which are involved in the development of obesity-related disorders.

Anti-Viral and Anti-Bacterial Activity
Infection by *Herpes simplex* virus ordinarily activates the cell protein nuclear factor κB (NF-κB). Resveratrol suppresses the activation of this transcription and apoptosis-related protein in vero cells. The study further
found that multiple viral protein products were reduced or completely blocked, as well as a reduction in viral DNA production was seen. A cell culture study found that resveratrol blocks the influenza virus from transporting viral proteins to the viral assembly site, hence restricting its ability to replicate. The effect was 90% when resveratrol was added six hours after infection and continued for 24 hours thereafter in vitro cells (Mayo MW, 1997). As a tiny molecule it penetrates the wall of almost any cell in an organism and also penetrates into the cell nucleus. There, resveratrol selectively switches on genes that aid the survival of an organism, like the sir2.1 DNA-repair gene. Using gene silencing, it switches off genes involved in the initiation and progression of disease, blocking replication of bacteria, viruses.

### Skin Care Ingredient

Resveratrol has ability to activate sirtuins on applying it topically to the skin. Small oral doses of resveratrol are known to be safe for millennia. When applied to the skin, even small amounts may create a high local concentration and produce sirtuin activation in skin cells. Topical application of resveratrol carries some uncertainties beyond its potential effect on sirtuins. On one hand, resveratrol is an antioxidant and anti-inflammatory, both of which is generally good for the skin. Indeed, in one study in mice, resveratrol reduced some indicators of free radical damage induced by ultraviolet light.

### Anti Aging Actions

Research started with an obvious theory that caloric restriction extends life by reducing cell damage from free radicals, which are generated when cells burn nutrients in the mitochondria to produce energy. Indeed, a reduction in free radical levels does appear to have some role. But in addition to this, Caloric restriction seems to trigger very specific cellular mechanisms of self-preservation whose biological role is to extend survival of the organism until food intake increases sufficiently to ensure successful reproduction. One biochemical pathway triggered by caloric restriction involves a class of enzymes called sirtuins (named after the corresponding gene sirt). The main role of sirtuins is to selectively regulate the activity of many key genes responsible for metabolism, cell defense, reproduction and other functions. Sirtuins are NAD-dependent histone deacetylases, the enzymes which inhibit the activity of genes by making DNA more tightly packed and thus less accessible for the cell's gene-copying machinery. Resveratrol is a potential sirtuin activator. This potential sprinkler of youth can activate sirtuins and extend lifespan in various species, from yeast to worms to rodents.

### Life Prolonging Activity

Resveratrol significantly extended the lifespan of the yeast *saccharomyces cerevisiae*. Later studies showed that resveratrol prolongs the lifespan of the worm *caenorhabditis elegans* and the fruit fly *drosophila melanogaster*. Resveratrol's supplementation with food extends vertebrate lifespan and delays motor and cognitive age-related decline could be of high relevance for the prevention of aging-related diseases in the human population. 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. This seems to function by lipase inhibition, reducing the absorption of fat through intestinal walls. A new report indicates that resveratrol activates SIRT1 and PGC-1α and thus improve functioning of the mitochondria. Only the “Trans” form of the molecule is capable of activating the mammalian SIRT1 gene in vitro.

Follow up studies, replicated the life extending benefits of resveratrol in mice, the first such demonstration in a higher animal. Preliminary results showed that obese mice provided with resveratrol lived an average of 15% longer than obese mice not provided the supplement. Both calorie restriction and resveratrol have been shown to prolong the life of all life forms, ranging from single-cell organisms (yeast cells) to more complex forms of life (fruit flies, roundworms) and warm-blooded mammals (laboratory rats).

### Other Actions

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 (Palamara AT and Parker JA et al., 2005). Again, this has not yet been tested in humans for any disease.

### Side Effects of Resveratrol

Resveratrol is a copper chelator and excessive chelation will impair the availability of copper which is needed for collagen formation and nerve regeneration. There is also evidence that supra-high dose resveratrol inhibits the absorption of folic acid (vitamin B9), an essential nutrient needed for DNA repair (Lemos C et al., 2007). Use of mega-doses of resveratrol (more than 500 mg) has initiated the side effects like anemia, achilles heel tendinitis, anxiety reactions, and numbness in the fingers.

### Safe Dose

Now an authoritative gene array study, conducted at the William S. Middleton Memorial Veterans Hospital and Lifegen Technologies in Madison, Wisconsin, showed that a dose of resveratrol ~343 milligrams per day (4.9 mg per kilogram of body weight) produces a gene activation profile similar to a calorie restricted diet. Supra-high doses (greater than 500 milligrams) are not required and may produce side effects.
Conclusion
It can be concluded that, the in vitro and in vivo (animal) studies have proved the potential of resveratrol. Further research in human beings will definitely make resveratrol a potential as well as the most priced molecule in improving the quality of life.

References


