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Review

# Beneficial action of resveratrol: How and why?

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ABSTRACT

Flavonoid resveratrol modulates the transcription factor NF-κB; inhibits the cytochrome P450 isoenzyme CYP1 A1; suppresses the expression and activity of cyclooxygenase enzymes; and modulates Fas/Fas-ligand-mediated apoptosis, p53, mammalian target of rapamycin, and cyclins and various phosphodiesterases. This increases the cytosolic cAMP that activates Epac1/CaMKKβ/AMPK/SIRT1/PGC-1α pathway, which in turn facilitates increased oxidation of fatty acids, mitochondrial biogenesis, mitochondrial respiration, and gluconeogenesis. Resveratrol triggers apoptosis of activated T cells and suppresses tumor necrosis factor-α, interluekin-17 (IL-17), and other proinflammatory molecules, and thus is of benefit in autoimmune diseases. In addition, resveratrol inhibits expression of hypoxia-inducible factor-1α and vascular endothelial growth factor, explaining its effective action against cancer. Brain-derived neurotrophic factor (BDNF) that is involved in the pathogenesis of obesity, type 2 diabetes mellitus, and metabolic syndrome is also altered in depression, schizophrenia, bipolar disorder, and autism. We noted that BDNF protects against cytotoxic actions of alloxan, streptozotocin, and benzo(a)pyrene. Resveratrol prevents bisphenol A-induced autism, type 2 diabetes mellitus, and metabolic syndrome, suggesting that it may augment BDNF synthesis and action. We also observed that BDNF levels are low in type 2 diabetes mellitus and that BDNF enhances production of antiinflammatory lipid, lipoxin A4, whose levels are low in diabetes mellitus. Thus, resveratrol may augment production of lipoxin A4. Resveratrol alters gut microbiota and influences stem cell proliferation and differentiation. These pleiotropic actions of resveratrol may explain the multitude of its actions and benefits.



## Introduction

The hypothesis that certain flavonoids such as resveratrol protect against dementia in elderly diabetic patients is interesting. The epidemic of obesity and type 2 diabetes mellitus, which is sweeping both the developed and developing countries, could be one reason for the increasing incidence of senile dementia. Consumption of high-fat/high-calorie diet, refined carbohydrates, and trans-fats and lack of adequate exercise are considered to be responsible for this epidemic of obesity and metabolic syndrome and consequent increase in the risk of coronary and cerebrovascular diseases, certain types of cancers, hypertension, non-alcoholic fatty liver disease, and Alzheimer's disease [1–3]. Increasing the consumption of dietary fiber, flavonoids, antioxidant micronutrients, and ω-3 polyunsaturated fatty acids is beneficial. An imbalance in the modern dietary habits as outlined above can lead to an increase in oxidative stress and endoplasmic reticulum (ER) stress that initiates the development of insulin resistance and onset of type 2 diabetes mellitus and Alzheimer's disease. Yorimitsu et al. [4] found that endomembranes progressively store misfolded proteins that

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cause ER stress, because unfolded proteins could trigger expression of chaperones resulting in autophagic cell death, including those of neuronal cells [5]. Autophagic activity dysregulation is related to obesity and type 2 diabetes mellitus [6]. ER stress and low-grade systemic inflammation seen in obesity lead to impairment of insulin sensitivity pathway, peripheral insulin resistance, and subsequent development of type 2 diabetes mellitus. This is supported by the work of Yin et al. [7], who found that adipocytes preloaded with the saturated fatty acid palmitate lead to ER stress and autophagy via protein kinase C–mediated signaling pathway independent of mammalian target of rapamycin (mTOR) [8].

## Resveratrol has antioxidant activity

One of the best ways to stem the epidemic of obesity, type 2 diabetes mellitus, and Alzheimer's disease is to restrict calorie intake and do regular exercise, which would lead to a decrease in ER stress. In this context, some of the beneficial actions of resveratrol seem tomimic several of the biochemical effects of calorie restriction. Resveratrol activates sirtuin 1 (SIRT1) [9] and peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α) and improves the functioning of the mitochondria [10,11]. Recent studies have revealed that resveratrol binds to tyrosyl transfer-RNA synthetase (TyrRS) to potentiate a signaling cascade driven by poly(ADP-ribose) polymerase 1 (PARP1)/NAD+ to activate p53 and AMPK by inhibiting SIRT1 [12]. Cells treated with resveratrol showed a 14-fold increase in the action of superoxide dismutase (SOD) that removes superoxide anion, a potent free radical [13]. SOD, by reducing superoxide, restores mitochondrial dysfunction to normal. Resveratrol, by activating SIRT1, causes migration of FOXO transcription factors to the nucleus [14], which stimulates FOXO3a transcriptional activity [15], and was shown to enhance the sirtuin-catalyzed deacetylation (activity) of FOXO3a. SOD is a target of FOXO3a, and MnSOD expression is strongly induced in cells overexpressing FOXO3a [16]. High expression of SOD but mild changes in catalase (CAT) and glutathione peroxidase (GPX) expression in cancer cells result in the mitochondrial accumulation of $H_2O_2$, which in turn induces cancer cell apoptosis [17]. It appears that both exercise and resveratrol induce disproportional upregulation of SOD, CAT, and GPX to bring about their beneficial actions in cancer.

In addition, resveratrol modulates the transcription factor NF-κB, inhibits the cytochrome P450 isoenzyme CYP1 A1, suppresses the expression and activity of cyclooxygenase enzymes, and modulates Fas/Fas-ligand-mediated apoptosis, p53, mTOR, and cyclins A, B1, and cyclin-dependent kinases cdk 1 and 2, which may also account for its benefits [18–21]. These actions of resveratrol [9–21] may be responsible for its benefit in Alzheimer's disease [22]. Resveratrol competitively inhibits various phosphodiesterases and thus increases cytosolic cAMP, which acts as a second messenger for the activation of the pathway Epac1/CaMKK-β/AMPK/SIRT1/PGC-1α, which facilitates an increase in oxidation of fatty acids, mitochondrial biogenesis, mitochondrial respiration, and gluconeogenesis [23,24] (see Fig. 1).

## Resveratrol has antiinflammatory activity

On exposure to different immune stimuli, native T cells are activated, undergo proliferation, and are made to undergo differentiation into three distinct functional subsets: $T_H1$ cells, $T_H2$ cells, and $T_H17$ cells. $T_H1$ cells produce interferon-γ and mediate protection against intracellular pathogens, whereas $T_H2$ cells produce interluekin-4 (IL-4), IL-13, and IL-25 and are concerned with the clearance of extracellular pathogens; $T_H17$ cells produce IL-17 and are needed to clear extracellular pathogens not effectively handled by either $T_H1$ or $T_H2$ cells. $T_H17$ cells defend the body against Gram-positive *Propionibacterium acnes*; Gram-negative *Citrobacter rodentium*, *Klebsiella pneumoniae*, *Bacteroides* spp., and *Borrelia* spp.; acid-fast *Mycobacterium tuberculosis*; and fungi such as *Candida albicans*. This widespread response to a variety of organisms suggests that $T_H17$ cells act as early responsive immunocytes to a number of pathogens that are not handled appropriately by $T_H1$- or $T_H2$-type immunity [25]. Thus, $T_H17$ cells bridge the gap between innate and adaptive immunity. IL-17-producing T cells have profound proinflammatory effects and induce tissue damage. IL-17-deficient mice develop attenuated collagen-induced arthritis and experimental autoimmune encephalomyelitis; increased levels of IL-17 have been observed in patients with rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and psoriasis evidence that strongly supports the contention that IL-17 and $T_H17$ cells play a significant role in autoimmune disorders [25–30]. The ability of resveratrol to trigger apoptosis in activated T cells and downregulate tumor necrosis factor-α, interferon-γ, IL-2, IL-9, IL-12, IL-17, macrophage inflammatory protein-1 alpha, and monocyte chemoattractant protein-1 may explain its potential in the treatment of inflammatory and autoimmune diseases [31–35].

Both hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) are overexpressed in many human tumors and their metastases, and are closely associated with a more aggressive tumor phenotype. Resveratrol inhibited the expression of these molecules, implying that it could be an effective anticancer therapy for the prevention of cancer and metastasis [36–38].

## Resveratrol is cytoprotective in nature

Increasing incidence of obesity and metabolic syndrome all over the world has been attributed not only to high-fat diet and lack of exercise but also to certain environmental factors such as bisphenol A (BPA), an endocrine disruptor present in plastic. A cross-sectional study performed in 76 of 139 environmentally exposed men, unselected Caucasian subjects enrolled by routine health survey at the "Federico II" University of Naples outpatient facilities, revealed that BPA and proinflammatory cytokine levels were significantly higher in subjects with visceral adiposity. BPA correlated with visceral obesity, triacylglycerols, glucose homeostasis, and inflammatory markers. At the multivariate analysis, WC and IL-6 remained the main predictors of BPA. These results support that BPA and other environmental factors may play a role in visceral-obesity-related low-grade chronic inflammation [39]. Similar association between BPA and autism has also been described [40].

In utero BPA exposure as a model environmental exposure has been shown to disrupt neurodevelopment and thus cause autism. Studies suggested that prenatal BPA induced lasting DNA methylation changes in the transcriptionally relevant region of the BDNF gene in the hippocampus and blood of BALB/c mice. Similar BDNF methylation changes were also reported in the cord blood of humans exposed to high maternal BPA levels in utero [41]. BDNF expression and DNA methylation are altered in several psychiatric disorders that are associated with early-life adversity, including depression, schizophrenia, bipolar disorder, and autism. BDNF is also involved in the pathogenesis of obesity, type 2 diabetes mellitus, and metabolic syndrome [42], indicating that environmental agents could alter the expression and