

Red Wine Consumption and Associated Health Benefits, the Resveratrol Story

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Resveratrol, 3,5,4'-trihydroxy-*trans*-stilbene, is a natural polyphenolic phytochemical that possesses a diverse array of biochemical and physiological actions, and offers promising therapeutic potentials. Although present in many plant species, it is found in only a select number of dietary sources, being absent in most fruits and vegetables,¹ thus is not a common component of the standard American diet. Primary dietary sources include grapes, red wine, peanuts and peanut butter.² Wine, however, is considered the predominant dietary source.³ Biochemically, the production of resveratrol is induced in the above mentioned plants in response to stressors, which may include injury, infection, water deprivation or UV irradiation. Its primary means of production, however, is in response to fungal infection.⁴ As a phytoalexin compound resveratrol is classified as an anti-fungicide, which confers disease resistance in susceptible hosts.³

In the last ten years an abundant number of scientific studies have documented the benefits of resveratrol consumption in the promotion and maintenance of optimal health. The focus of a majority of these studies has been on its cardioprotective benefits. Other favorable attributes of resveratrol have also been acknowledged, and its range of benefits noted to encompass numerous protective effects, including hepatic protection, protection against inflammation, neuronal injury and degeneration, and against viral insult.⁵

Cardiovascular Health

Resveratrol is viewed as a major cardioprotective constituent in red wine.⁶ In the French population a high consumption of red wine is associated with a decreased risk of morbidity and mortality from coronary heart disease, a phenomenon referred to as the “French paradox”.⁷ The positive attributes of resveratrol on cardiovascular health are broad, and

encompass multiple modalities of health-promoting actions. Included in these actions are its vasorelaxative properties, its benefits on inflammation, its ROS scavenging abilities, as well as its anti-apoptosis and angiogenic properties.⁴

In both acute and chronic models of cardiovascular disease, resveratrol demonstrated cardiac protection, which was attributed to its “preconditioning effect”.⁴ Its use has also been confirmed to modulate cellular vascular function, as well as to inhibit LDL oxidation. Additionally, administration of *trans*-resveratrol was demonstrated to result in a reduction in both LDL and triglycerides,⁸ as well as a 7% increase in HDL,⁹ which is in agreement with other studies demonstrating the hypolipidemic properties of this stilbene. These beneficial cardiovascular features are postulated to be mediated through the activation of the poly-ADP-ribose polymerases (PPAR), specifically PPAR α ,^{9,10} which is the isoform involved primarily in both fatty acid and lipid importation and catabolism, as well as in the activation of genes involved in fatty acid oxidation.⁹ At very low concentrations, as is typical in the daily diet, resveratrol is speculated to offer cardioprotection.¹¹ This phenomenon has been referred to as the “French Paradox”, which correlates wine intake with a low incidence of CVD mortality, despite an increased intake of saturated fat.¹² *Trans*-resveratrol has also been shown to suppresses platelet aggregation; reduce myocardial damage during ischemia-reperfusion, and to inhibit LDL oxidation.^{11, 13} The suppression of platelet aggregation by resveratrol was validated in one study, whereby aggregation was induced by a stimulus, being either collagen, thrombin or ADP. Under these conditions resveratrol administration was demonstrated to inhibit platelet aggregation.¹⁴ It was also demonstrated to inhibit apoptotic cell death.¹⁵ Other studies have observed similar results, with resveratrol demonstrating a protective effect against induced apoptotic cell death on aortic endothelial cells.¹⁶ It was also shown to attenuate the generation of hydrogen peroxide (H₂O₂), and to result in a significant decrease in DNA damage.¹⁷ At higher doses it was demonstrated to facilitate apoptotic cell death, and possess anti-carcinogenic properties, thus due to this action it has

consequently been classified as a chemopreventative agent.¹⁵ Corroborating this action, another study specifically indicated that administration of resveratrol resulted in apoptosis, in addition to a corresponding release of cytochrome c and apoptotic protease-activating factor-1 (APAF-1).¹⁸ This specific action has been further classified, with the proposition that resveratrol's action is in the activation of the caspase cascade, specifically caspase-8.¹⁹ The caspase cascade is an essential component of cellular apoptosis, and caspase-8 specifically is classified as an initiator of the caspase cascade.²⁰

In addition to the affirmative benefits noted above, the correlation between resveratrol consumption and cardiovascular health has also been attributed to its ability to improve nitric oxide bioavailability. The molecule nitric oxide has been associated with cardiovascular health, primarily due to its wide range of biological properties, which function in the preservation of vascular homeostasis. Nitric oxide is believed to play a critical role in cardiovascular preconditioning.^{21,22} The properties possessed by resveratrol are said to include the "modulation of vascular dilator tone, regulation of local cell growth, and protection of the vessel from injurious consequences of platelets and cells circulating in blood,"²³ as well as "defense against ischemic-reperfusion injury, promotion of vasorelaxation, protection and maintenance of intact endothelium, anti-atherosclerotic properties, inhibition of low-density lipoprotein oxidation, and suppression of platelet aggregation".²⁴ Additionally, expanding evidential support has correlated the constitutive expression of nitric oxide with a cardio-protective role.^{25,26} Heart preconditioning with resveratrol was demonstrated to provide cardioprotection, as well as to reduce the size of myocardial infarction and apoptosis of cardiomyocytes. This cardioprotective effect was completely abolished with the use of either a NO inhibitor or an inducible NO synthase blocker, affirming resveratrol's beneficial action.²⁷ A separate study associated resveratrol's action to a beneficial effect on the human endothelial nitric oxide synthase (eNOS) enzyme activity and promoter, which was demonstrated to be significantly enhanced with consumption.²⁸

Cumulatively, all effects taken into consideration, dietary supplementation of resveratrol has demonstrated a supportive role in cardiovascular health through a diverse range of mechanisms, thus making it a beneficial adjunct for cardiovascular wellbeing.

Benefits in Inflammatory Pathologies

Both cyclooxygenase (COX)-1 and COX-2 are important enzymes in the production of the prostanoid class of compounds, which includes prostaglandins, prostacyclin and thromboxane.²⁹ While COX-1 is found in most mammalian cells and is considered a constitutively expressed enzyme, it is upregulated with inflammation.³⁰ Conversely, COX-2 is an inducible enzyme, produced specifically in response to cellular signals, including mitogens and growth factors.³¹ Zarraga, *et al.* have postulated that a correlation exists between the expression of COX-2, and the stimuli implicated in the development of disease pathologies, specifically atherosclerosis. These pathologies and the correlated stimuli include the production or generation of free radicals,³² tumor necrosis factor, interleukin-1,³³ platelet-derived growth factor,³⁴ as well as increased shear stress on the arterial wall.³⁵ With resveratrol administration, a non-selective inhibition of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)^{36,37,38} has been demonstrated, thus signifying an anti-inflammatory effect. In regards to COX-2, resveratrol was demonstrated to inhibit COX-2 enzyme activity in a dose-dependent manner.⁵ Other studies have indicated that resveratrol acts as a suppressor of COX-2 expression, rather than an inhibitor. In a separate *in vitro* study resveratrol's anti-inflammatory effect was confirmed by its inhibition of the production of reactive oxygen species (ROS), phospholipase A₂ activity, PGE₂ synthesis and the release of arachidonic acid.³⁹ A successive study confirmed this action, indicating that resveratrol, in a dose dependent manner, inhibited the arachidonate-dependent synthesis of thromboxane B₂, hydroxyheptadecatrienoate (HHT) and 12-hydroxyeicosatetraenoate (12-HETE).⁴⁰ In addition to inhibiting the induction of COX-2, a successive study established that with resveratrol supplementation, an inhibition of the ROS induced

formation of lipopolysaccharide and phorbol esters (PMA), along with a marked reduction in the synthesis of prostaglandins occurred.³⁶ Other studies have noted a significantly lower level of edema, inflammatory activity and necrosis with resveratrol use.⁴¹ In a separate animal study, using chronic ethanol administration as a stimulus, resveratrol intake was noted to inhibit lipid peroxidation, as well as to ameliorate SOD, glutathione peroxidase (GPx) and catalase (CAT) activities in the liver. In the ethanol only group (without resveratrol), the activities of hepatic SOD, GPx, and CAT were reduced, implicating a protective, antioxidant effect of resveratrol administration.⁴² Taken together these results indicate resveratrol's potent anti-inflammatory activity.

Gastrointestinal Benefits of Resveratrol

Gastrointestinal diseases, including inflammatory bowel disease, may be characterized by proinflammatory cytokines, resulting in associated damage to corresponding tissues, and a neuronal loss in inflamed mucosa. Correspondingly, the cholinergic protective mechanisms are susceptible to damage from the ensuing inflammatory responses.⁴³ Due to its anti-inflammatory properties, resveratrol use has demonstrated beneficial attributes for gastrointestinal health. In one study utilizing an acute colitis animal model, resveratrol was demonstrated to modulate apoptosis, as well as to "significantly attenuate the damage score" and to correct the associated morphological disturbances.⁴⁴ A separate study indicated that resveratrol supplementation improved induced acute gastric lesions, as well as prohibited the progression of these lesions into ulcers.⁴⁵ An additional study demonstrated resveratrol's beneficial attributes in the prevention of damage to the gastrointestinal mucosa in experimentally induced necrotizing enterocolitis (NEC). In this study resveratrol was demonstrated to attenuate the release of inducible nitric oxide synthase (iNOS) and to preserve both mucosal integrity and epithelial structure.⁴⁶ Other studies have conclusively demonstrated resveratrol's benefits in significantly alleviating oxidative stress, which was evidenced by a reduction in TNF-alpha levels, with a successive reduction in the ensuing damage resulting from

experimentally induced colitis. In colonic cells it was also shown to normalize PGE2 production and to stimulate apoptosis.^{44,47}

Additional Cellular Protective Effects of Resveratrol

Anti-Aging Benefits

In addition to extending the replicative lifespan of yeasts, *C. elegans* and *Drosophila*, resveratrol has also demonstrated beneficial attributes in improving human cell survival. The anti-aging benefits of resveratrol have been associated with the fact that it functions as a sirtuin activator.^{48,49} Thus, not surprisingly it has been referred to as a sirtuin activating compound or STAC.⁴⁹ The Class III protein deacetylases, silent information regulator 2 (Sir2) family proteins, classically known as sirtuins, and referred to as the SIRT genes in mammals, are conserved among species, from prokaryotes to mammals.⁵⁰ Humans contain seven sirt genes, denoted as SIRT 1-7.^{51, 52} In a broad classification they function to deacetylate transcription factors (DNA binding proteins that control the processing of DNA to RNA), including forkhead box class O transcription factors (FOXOs), as well as p53,^{53, 54, 55, 56, 57} an important factor in signaling pathways involving cell surveillance following cellular stress,⁵⁸ and nuclear factor Kappa B^{59, 60, 61} (NF-KappB). In humans and yeasts, the sirtuins function specifically to catalyze NAD-dependent histone deacetylations, thus for this reason their action has been linked to metabolism.^{62, 63, 64} In addition to anti-aging properties, by virtue of their regulation of programmed cell death, they have also been associated with the regulation of gene silencing,^{65,66} DNA repair mechanisms^{67, 68}, and ribosomal DNA recombination.^{69, 70, 71} Studies utilizing *in vitro* models have demonstrated that SIRT1 provides cellular protection against amyloid-beta-induced ROS production and DNA damage, subsequently resulting in reduced apoptotic cell death.⁷² In other models it has been shown to increase the longevity of myocytes (heart muscles cells) in weakened hearts, by virtue of sirtuins activation.⁷³ SIRT1 has also been shown to regulate neuronal survival, gluconeogenesis, lipolysis, β -cell survival, and insulin secretion by interacting with a number of target proteins.⁷⁴ As such, sirtuin activation has

been likened to the effects of a restricted calorie diet, which is known to extend life-span in mammals. In fact in one animal study utilizing resveratrol and a gene expression assay, of the 1,029 genes ($P \leq 0.01$) in the heart demonstrating a significant alteration in expression with aging, resveratrol opposed 947 (92%) of age-related changes in gene expression. Of these, 522 represented highly significant differences in expression between the control and the resveratrol groups ($P \leq 0.01$).⁷⁵

Antioxidant Properties

In addition to its antiaging properties, resveratrol has also been shown to be a potent antioxidant. The mechanism has been demonstrated to result from its ability to increase the cellular content of manganese superoxide dismutase (MnSOD). MnSOD is essential for life, and overexpression has been shown to protect against pro-apoptotic stimuli and ischemic damage,⁷⁶ as well as to offer neuroprotective characteristics. In a human cell line (MRC-5) two weeks exposure to resveratrol was demonstrated to increase the MnSOD protein level 6-fold, and the activity level 14-fold, resulting in a highly specific upregulation of MnSOD.⁷⁷ MnSOD is considered the first line of defense against oxidative stress.⁷⁸ A decline in MnSOD activity has been associated with various diseases, including cardiovascular impediments⁷⁹, vascular oxidative stress, endothelial dysfunction, aging⁸⁰, Hutchinson-Gilford Progeria Syndrome (progeria)⁸¹, asthma⁸², and transplant rejection.⁸³

Anti-angiogenesis properties.

Resveratrol has been shown to inhibit the abnormal formation of new blood vessels, a process known as angiogenesis. Tumor growth is dependent upon angiogenesis, and disruption of blood vessel growth inhibits tumor expansion and its metastasis⁸⁴, thus angiogenesis is considered a crucial step for the growth and metastasis of cancers. In animal models resveratrol administration was demonstrated to directly inhibit endothelial cell growth, as well as to inhibit endothelial cell attachment to the basement membrane components fibronectin and laminin.⁸⁵ A separate study observed angiogenesis inhibition of multiple myeloma by resveratrol via its

regulation of expression and secretion of both growth factors (VEGF and vFGF) and metalloproteinases (MMP)-2 and MMP-9 mRNA.⁸⁶

Post menopausal benefits.

Resveratrol was found to exhibit bone-protective effects equivalent to those exerted by hormone replacement therapy and to decrease the risk of breast cancer in both *in vivo* and *in vitro* models. Resveratrol is therefore anticipated to be highly effective in management of postmenopausal osteoporosis without an increased risk of breast cancer.⁸⁷

Although the research on resveratrol is still in infancy, as the literature is continually documenting additional benefits, specifically of the *trans* form, its use illustrates promising advantages for multiple scenarios. The *trans* form is the naturally available form, which may be converted to the *cis* form via exposure to ultraviolet light.⁸⁸ Safe dosage is estimated to be between the ranges of 200 to 2000 mg per day. Of importance to note is that all resveratrol is not equivalent as various degrees of purity are commercially available. Furthermore, although resveratrol is reasonably well absorbed in humans, it has a low bioavailability,^{89, 90} and is cleared rapidly via both glucuronidation and sulfation pathways.^{91, 92} As such modulating (slowing) the metabolism rate of oral resveratrol administration is a prudent consideration.

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These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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