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DOSE-DEPENDENCY OF RESVERATROL IN PROVIDING HEALTH BENEFITS

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□ This review describes the dose-dependent health benefits of resveratrol, a polyphenolic antioxidant that is found in a variety of foods, especially grape skin and red wine. Resveratrol provides diverse health benefits including cardioprotection, inhibition of low-density lipoprotein, activation of nitric oxide (NO) production, hindering of platelet aggregation [32] A.A.E. Bertelli, D.E. Giovannini, R.L. Caterina, W. Bernini, M. Migliori and M. Fregoni *et al.*, Antiplatelet activity of *cis*-resveratrol, *Drugs Exp Clin Res* 22 (1996), pp. 61–63. View Record in Scopus | Cited By in Scopus (111) and promotion of anti-inflammatory effects. Studies have shown that at a lower dose, resveratrol acts as an anti-apoptotic agent, providing cardioprotection as evidenced by increased expression in cell survival proteins, improved post-ischemic ventricular recovery and reduction of myocardial infarct size and cardiomyocyte apoptosis and maintains a stable redox environment compared to control. At higher dose, resveratrol acts as a pro-apoptotic compound, inducing apoptosis in cancer cells by exerting a death signal. At higher doses, resveratrol depresses cardiac function, elevates levels of apoptotic protein expressions, results in an unstable redox environment, increases myocardial infarct size and number of apoptotic cells. At high dose, resveratrol not only hinders tumor growth but also inhibits the synthesis of RNA, DNA and protein, causes structural chromosome aberrations, chromatin breaks, chromatin exchanges, weak aneuploidy, higher S-phase arrest, blocks cell proliferation, decreases wound healing, endothelial cell growth by fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor, and angiogenesis in healthy tissue cells leading to cell death. Thus, at lower dose, resveratrol can be very useful in maintaining the human health whereas at higher dose, resveratrol has pro-apoptotic actions on healthy cells, but can kill tumor cells.

INTRODUCTION

A growing body of evidence supports that nutrition plays a major role in maintaining a healthy heart. A proper diet containing a variety of grains, fruits, vegetables and foods that are low in saturated fat, *trans* fat and cholesterol, help maintain a healthy heart. Coronary heart disease (CHD) is one of the major causes of death worldwide. Epidemiologic and human intervention studies have shown the inverse relationship between the consumption of plant-based diets and deaths attributed to heart disease. Most dietitians and nutritionists around the world are recommending an increase in the consumption of plant foods for the prevention of

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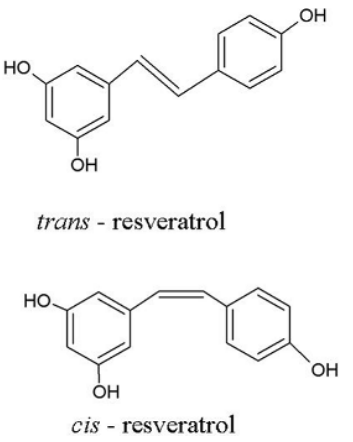

FIGURE 1. Chemical structure of *cis*-resveratrol and *trans*-resveratrol.

CHD. Certain foods are well known for their ability to protect human health from CHD. Grape is the most well known among them and has been used in medicinal science from the time immemorial. *Ayurveda*, one of the ancient medicinal books of Hindus, described "darakchasava" (fermented juice of red grapes) as a cardio tonic (Paul *et al.* 1999). Grape juice or red wine was also described as a "gift of god" in The Bible. Resveratrol is a naturally occurring phytoalexin present in grape skin. Its chemical name is trans-3,5,4'-trihydroxy stilbene (Figure 1). Resveratrol occurs in two isoforms *cis* and *trans* – resveratrol, but *trans*- resveratrol is more biologically active than its *cis* isoform. In last few decades, resveratrol gained the attention of scientists worldwide due to its anti-cancer, anti-inflammatory, blood-sugar-lowering and other beneficial cardiovascular effects. Resveratrol has been reported to show these properties in experimental mouse and rat models. Most of these results have yet to be replicated in humans. In this article we will discuss the sources, health benefits, molecular targets and dose dependency in delivering health benefits of resveratrol.

SOURCES OF RESVERATROL

Resveratrol was first identified as the principal active ingredient from the dried roots of *Polygonum cuspidatum,* mainly found in Japan and China. Polygonum extract has been used in Japanese and Chinese traditional medicine to treat fungal infection, various skin inflammations, liver disease and cardiovascular disease (Arichi *et al.* 1982; Vastano *et al.* 2000). Grape skin is the main source of resveratrol. In addition to grapes, resveratrol is present in a large variety of fruits such as cranberry, mulberry, lingberry, bilberry, partridgeberry, sparkleberry, deerberry, blueberry, jackfruit, peanut and also in a wide variety of flowers and leaves including gnetum, butterfly orchid tree, white hellebore, scots pine, corn lily, eucalyptus, spruce etc.

TABLE 1: The amount of resveratrol found in natural foods.

Source	Resveratrol concentration
100% Natural peanut butter	~0.65 μg/g
Bilberries	~16 ng/g
Blueberries	~32 ng/g
Boiled peanuts	~5.1 μg/g
Cranberry raw juice	~0.2 mg/L
Dry grape skin	~24.06 μg/g
Grapes	0.16–3.54 μg/g
Peanut butter	0.3–1.4 μg/g
Peanuts	0.02–1.92 μg/g
Pistachios	0.09–1.67 μg/g
Ports and sherries	<0.1 mg/L
Ref grape juice	~0.50 mg/L
Red wines	0.1–14.3 mg/L
Roasted peanuts	~0.055 μg/g
White grape juice	~0.05 mg/L
White wines	<0.1–2.1 mg/L

Resveratrol is also synthesized in response to environmental stressors that include water deprivation, UV irradiation and especially fungal infection (Das and Maulik 2006). Apart from these naturally occurring substances, red wine and white wine also contain resveratrol. All of the above mentioned substances demonstrate their cardioprotective activities (Baur *et al.* 2006) due to the presence of resveratrol. Table 1 shows the amount of resveratrol found in natural foods (Dudley *et al.* 2008a).

HEALTH BENEFIT OF RESVERATROL

It is now well known that resveratrol protects human health by diverse mechanisms. It received importance during early nineties in the context of "French paradox"; the phenomena wherein certain population of France, in spite of eating a regular high fat diet, was less susceptible to heart diseases (Richard 1987). The apparent cardioprotection was attributed to the regular consumption of moderate doses of red wine rich in resveratrol in their diet (Kopp 1998)[14] P. Kopp, Resveratrol a phytoestrogen found in red wine a possible explanation for the conundrum of the 'French paradox', *Eur. J. Endocrinol.* 138 (1998), pp. 619–620. Full Text via CrossRef | View Record in Scopus | Cited By in Scopus (118). Resveratrol is a natural antioxidant; it can scavenge some intracellular reactive oxygen species (ROS). Although resveratrol is not a potent antioxidant *in vitro*, it functions as a potent antioxidant *in vivo*. Most likely the *in vivo* antioxidant property of resveratrol is derived from its ability to increase nitric oxide (NO) synthesis, which in turns acts as an antioxidant. It has been shown that resveratrol induces NO synthesis in case of ischemic reperfused heart, brain and kidney and lower the oxidative stress (Hattori *et al.* 2002; Cadenas and Barja 1999). Certain wines, grape

juices, especially grape skins can provide cardioprotective effects due to presence of resveratrol. Studies have shown that resveratrol protects perfused rat hearts through an increase in inducible nitric oxide synthase (iNOS) expression and this effect is abolished in case of iNOS knockout mice (Hattori *et al.* 2002; Imamura *et al.* 2002). It was also shown that resveratrol provides cardioprotection via upregulation of catalase activity in the myocardium. Resveratrol has been found to pharmacologically precondition hearts by a NO-dependent manner (Hattori et al., 2002 R. Hattori, H. Otani, N. Maulik and D.K. Das, Pharmacological preconditioning with resveratrol: role of nitric oxide, *Am. J. Physiol.* 282 (2002), pp. H1988–H1995. View Record in Scopus | Cited By in Scopus (75)Hattori *et al.* 2002; Imamura *et al.* 2002). In another study, Das et al. (2005a) showed that resveratrol –induced preconditioning was derived through the upregulation of the iNOS–vascular endothelial growth factor (VEGF)–VEGF receptor-2/kinase insert domain-containing receptor (KDR)–endothelial nitric oxide synthase (eNOS) pathway. A number of studies have successfully demonstrated that in rat myocardial infarction (MI) model resveratrol significantly upregulates the protein expression profiles of vascular endothelial growth factor (VEGF) and its tyrosine kinase receptor fetal liver kinase-1 (Flk-1), which in turn ameliorates myocardial damage (Fukuda *et al.* 2006). Several studies from our laboratory have shown that resveratrol protects mammalian hearts from ischemia/reperfusion-induced injury. Resveratrol improves postischemic ventricular function, reduces myocardial infarction and cardiomyocyte apoptosis, activates survival signal, and reduces death signal (Das *et al.* 2005b; Das and Maulik 2006; Dudley *et al.* 2008a, Dekkers *et al.* 2008). It has been also shown that resveratrol increases GLUT-4 expression and reduces endothelin expression in ischemic-reperfused hearts of Zucker obese rats in the presence or absence of glucose intake (Lekli *et al.* 2008). This study indicates that resveratrol could provide protection against obesity related cardiac injury.

Resveratrol regulates the redox homeostasis in mammalian system by maintaining the amounts of several antioxidant enzymes, including glutathione peroxidase, glutathione–*S*-transferase and glutathione reductase (Yen *et al.* 2003). It is also known that resveratrol prevents low density lipoprotein (LDL) oxidation (Frankel *et al.* 1993). There is evidence that resveratrol is a potent inhibitor of the oxidation of polyunsaturated fatty acids (PUFA) found in LDL. In fact, resveratrol was shown to be more potent than flavonoids in preventing copper-catalyzed oxidation, thus preventing oxidative modification of LDL (Frankel *et al.* 1993). Hebbar et al. (2005) showed that high doses (0.3, 1.0 and 3.0 g/kg day) of resveratrol upregulates phase II and antioxidant genes in female and male rats. Due to high rate of oxygen consumption and low levels of antioxidant defense enzymes, the brain and the heart are particularly vulnerable to

hypoxic conditions and oxidative stress injuries. Heme oxygenase-1 (HO-1) has been shown to be neuroprotective (Dore 2002), it degrades the pro-oxidant heme into biliverdin/bilirubin, iron and carbon monoxide. Bilirubin can scavenge free radicals. Carbon monoxide is a cell cycle modulator and vasodilator. It has been reported that CO provides anti-inflammatory and antiapoptotic effects via nuclear factor kappa B (NF(B) regulation (Kim *et al.* 2006). Resveratrol induces HO-1 in primary neuronal cultures (Zhuang *et al.* 2003) and aortic smooth muscle cells (Juan *et al.* 2005) at low concentrations (1–10 mM). At higher concentrations (>20 mM), NF(B activation was suppressed and HO-1 was inhibited. Moderate resveratrol or red wine rich in resveratrol intake (presumably low concentration) could, therefore, have a considerable neuro-protective and vascular-protective effect against oxidative stress.

Resveratrol inhibits platelet aggregation, which is a major contributor in the process of atherosclerosis (Olas *et al.* 2001; Orsini *et al.* 1997). Platelets through the activation of the process of thrombus formation and their aggregation could set into motion the process of vascular occlusion. A dose dependent decrease in platelet aggregation was shown with resveratrol treatment (Soleas *et al.* 1997). Resveratrol (0.15 and 0.25 micromole/l) was shown to inhibit collagen-induced platelet activation accompanied by [Ca^{+2}] immobilization, thromboxaneA2 formation, phosphoinositide breakdown, and protein kinase C (PKC) activation (Shen *et al.* 2007).

Resveratrol has been shown to possess potential anticancer activity in various cancer cells at the initiation, promotion, and progression stages (Jang *et al.* 1997). High dose resveratrol (50 mM) has been shown to induce cell death in mouse xenograft models of human neuroblastoma cells (SH-SY5Y, NGP, and SK-N-AS) (van Ginkel *et al.* 2007). Moreover, 48 h exposure of 100 mM resveratrol induced cell death in human colorectal cancer cells (DLD1 and HT29 cells) (Trincheri *et al.* 2007). Inhibitory effects of resveratrol against breast cancer progression has been reported in both estrogen-positive (MCF-7) and estrogen-negative (MDA-MB-231) breast cancer cells as a result of 1 mM resveratrol treatment *in vitro* and in nude mice inoculated with any of these cell lines. Ten mg per kg body weight (BW) resveratrol treatment for 2 days reduced the cancer progression (Su *et al.* 2007). Resveratrol is also well known to possess anti cancer properties in animal model. It was shown that 625 mg/kg body wt resveratrol reduced the progression of prostate cancer in transgenic adenocarcinoma prostate (TRAMP) mice (Harper *et al.* 2007). Bhardwaj et al. (2007) showed that 50 (M resveratrol could reduce the proliferation of human multiple myeloma. Most of its anticancer properties are attributed to its ability to induce apoptosis in cancer cells (Abd El-Mohsen *et al.* 2006; Trincheri *et al.* 2007; Bhardwaj *et al.* 2007; Sun *et al.* 2006; Busquets *et al.* 2007). For example, resveratrol induces loss of mitochondrial mem-

brane potential, leading to release of cytochrome C and Smac/Diablo, and subsequent activation of caspase-9 and caspase-3 (van Ginkel *et al.* 2007). In addition to these mechanisms, resveratrol can also induce cell cycle arrest at G0/G1 phase and reduce the expression of cell growth factors in human prostate cancer cell lines (Benitez *et al.* 2007). Resveratrol was also shown to activate proapoptotic Bax, p53, and p21waf in T-cell acute lymphoblastic leukemia cells (Hwang *et al.* 2007), and to reduce the levels of antiapoptotic Bcl-xL, Bcl-2, cyclin D1, and TNF receptor-associated factor (Benitez *et al.* 2007; Bhardwaj *et al.* 2007; Athar *et al.* 2007). In case of human breast cancer cells resveratrol inhibited the anti-apoptotic phosphatidylinositol 3_-kinase (PI3K)/Akt pathway (Cecchinato *et al.* 2007), and activated the Forkhead transcription factor (FOXO3a) (Su *et al.* 2007), which mediates cellular apoptosis through the activation of proapoptotic genes (Su *et al.* 2007). In addition, in earlier studies, resveratrol had been proposed to downregulate the expression of tumorigenic nuclear factor NF(B and its regulated proapoptotic gene products as well as growth factors in multiple myeloma cells (Sun *et al.* 2006).

In addition to its anticancer activity, resveratrol has displayed beneficial activity against inflammatory responses via inhibition of cyclooxygenase 1 (COX1) and cyclooxygenase (COX2) expression (Kundu *et al.* 2006). Resveratrol was reported to reduce the production of prostaglandin E2 (PGE2) and the formation of ROS in lipopolysaccharide (LPS)-activated microglial cells (Candelario-Jalil *et al.* 2007; Kim *et al.* 2007). Moreover, resveratrol was reported to suppress the activity of T- and B-cells, and macrophages (Sharma *et al.* 2007). Singh et al (2007) showed that resveratrol induced both caspase-dependent and caspase-independent apoptosis in activated T-cells in experimental allergic encephalomyelitis- induced mice. One study from our own laboratory showed that resveratrol possesses analgesic property by inhibition of COX1 and COX 2 (Bertelli *et al.* 2008).

Resveratrol also possesses neuroprotective properties. It has been reported that resveratrol could protect against Huntington's disease (Parker *et al.* 2005), Alzheimer's disease (Marambaud *et al.* 2005) and Parkinson's disease (Karlsson *et al.* 2000).

RESVERATROL AND LONGEVITY

A significant number of reports exist in the literature indicating that resveratrol can activate the longevity assurance genes, Sirtuins (SirTs) (Miyazaki *et al.* 2008; Borra *et al.* 2005; Kaeberlein *et al.* 2005; Jiang 2008; Guarente 2007). Resveratrol was shown to extend the life span in Drosophila (Griswold *et al.* 2008) and C. elegans (Gruber *et al.* 2007) as well as in vertebrates such as short-lived fish Northobranchius (Terzibasi *et al.* 2007). Bauer et al. showed for the first time that resveratrol could extend life span in case of mammals also (Baur *et al.* 2006), In this study,

high-calorie diets (60% of calories from fat) induced obesity, triggering an inflammatory response and comorbidities, such as diabetes and atherosclerosis, which decreased the life span in case of middle-aged (1-year-old) mice, but resveratrol treatment (22.4 mg/kg/day) along with the high-fat diets extended the life span by inducing Sirt1 similar to calorie-restricted animals with greater SIRT1 coexpression (Nisoli *et al.* 2005). Evidence is available to show the positive effects of resveratrol and SIRT1 activation on several age related disorders including type 2 diabetes, cardiovascular disease, neurodegeneration, and inflammation (Baur and Sinclair. 2006; Pearson *et al.* 2008; Lagouge *et al.* 2006; Milne *et al.* 2007). Resveratrol increases longevity through SirT1, which is activated with NAD^+ supplied by an anti-aging enzyme pre B cell-enhancing factor (PBEF). SirT1 interacts with an anti-aging transcription factor, forkhead box protein O1 (FoxO1), which is negatively regulated by Akt. We have shown in one of our recent studies that resveratrol induced the activation of SirT1, SirT3, and SirT4, and the phosphorylation of FoxO1 and fprkhead box protein O3a (FoxO3a) as well as PBEF proteins (Mukherjee *et al.* 2009). This study also showed that red wine and white wine induced SirT1, SirT3, SirT4 and PBEF proteins as well as the phosphorylation of FoxO1 and FoxO3a due to the presence of the common component resveratrol (Mukherjee *et al.* 2009). Thus, resveratrol and red wine can provide protection against age-related cardiac diseases.

MOLECULAR TARGETS OF RESVERATROL

In the vast majority of cases, resveratrol displays inhibitory/stimulatory effects in the micromolar range, which is potentially attainable pharmacologically. It appears that resveratrol, as a pharmacological agent, has a wide spectrum of targets. The biological activities of resveratrol may thus be dependent on its simultaneous activities on multiple molecular targets. Cancer and inflammation are critically linked, and among the enzymes that synthesize proinflammatory mediators from arachidonic acid are the cyclooxygenases and lipooxygenases (COX and LOX) (Aggarwal *et al.* 2006). Different studies demonstrate that resveratrol can inhibit both 5-lipooxygenase and cyclooxygenase enzymes. The synthesis of proinflammatory molecules by COX and LOX is an important step for the initiation of tumorogenesis. Thus, the inhibitory effects of resveratrol on COX/LOX catalytic activities are highly relevant to cancer chemoprevention (Subbaramaiah and Dannenberg 2003). Kinase is the other enzyme family, which is moderated by resveratrol. It is known that resveratrol can inhibit tyrosine kinase ($p56^{lck}$) and serine/threonine kinase (PKC, with both (and (isoforms present in a mixture) (Jayatilake *et al.*, 1993). Resveratrol can inhibit both protein kinase C (PKC) and protein kinase D (PKD). Inhibition of PKC isoforms by resveratrol is related to growth inhibition and induction of apoptosis in various cancer cell mod-

els, including gastric cancer cells (Atten *et al.* 2005) and prostate cancer cells (Stewart and O'Brian 2004). The inhibition by resveratrol of the activities of receptor tyrosine kinases and Src kinase may be relevant to its antitumor activity. Study on HER-2/neu transgenic mice has further expanded the concept that chemopreventive activity of resveratrol is due to targeting tyrosine kinase cascades (Muller *et al.* 1988). Another major target of resveratrol is the mitogen-activated protein kinase (MAPK) family, including the extracellular signal regulated kinases (Erk1/2) and the stress activated kinases JNK1/2 and p38 MAPK. Resveratrol (30–50 (M) inhibited endothelin-1 induced Erk1/2 enzymatic activity and Erk1/2, JNK and p38 MAPK phosphorylation in coronary artery smooth muscle cells (El-Mowafy and White 1999), thus suggesting a partial mechanism for the beneficial cardiovascular effects of resveratrol. Since resveratrol also acts as a cancer chemopreventive molecule and PI3K/PKB virtually always activated in tumors, it can be expected that it resveratrol might have an impact on the PI3K/PKB signaling pathway (Hennessy *et al.* 2005). Further studies on the inhibitory potential of resveratrol on cancer cells might eventually define PI3K as a target of resveratrol in cancer. The improvement of insulin sensitivity due to long-term treatment with resveratrol in mice was associated to AMPK phosphorylation (Baur *et al.* 2006). Furthermore, in a recent report resveratrol was shown to stimulate glucose transport in C_2C_{12} myotubes via adenosine monophosphate-activated protein kinase (AMPK) activation (Park *et al.* 2007). Sirtuin is another potential target of resveratrol. Resveratrol activates Sirt1, which is responsible for its life extending properties (Kaeberlein *et al.* 2005; Borra *et al.* 2005). Besides the action of resveratrol on COX/LOX, kinases and sirtuins, several other resveratrol targets have been identified, such as ribonucleotide reductase, adenylyl cyclase, quinone reductase 2, aromatase and DNA polymerases (Pirola and Frojdo 2008) (Figure 2).

DOSE DEPENDENCY OF RESVERATROL

From the previous discussion it should be clear that resveratrol protects human health through chemoprevention to cardioprotection. Resveratrol provides protection against cancer, cardiovascular diseases, ageing related diseases and also possess chemoprotective, neuroprotective, anti-inflammatory properties. In case of myocardial injury and ageing related diseases, resveratrol protects cells from apoptosis thereby working as an anti-apoptotic agent whereas in cancer prevention, resveratrol kills the cancer cell by inducing apoptosis, thus working as a pro-apoptotic agent. So resveratrol can function both as pro-apoptotic and anti-apoptotic agents. Here the question arises, how resveratrol can function as both pro-and anti-apoptotic agents?

Careful review of the studies on cancer prevention with resveratrol reveals that in each case, resveratrol was used at high concentration/dose

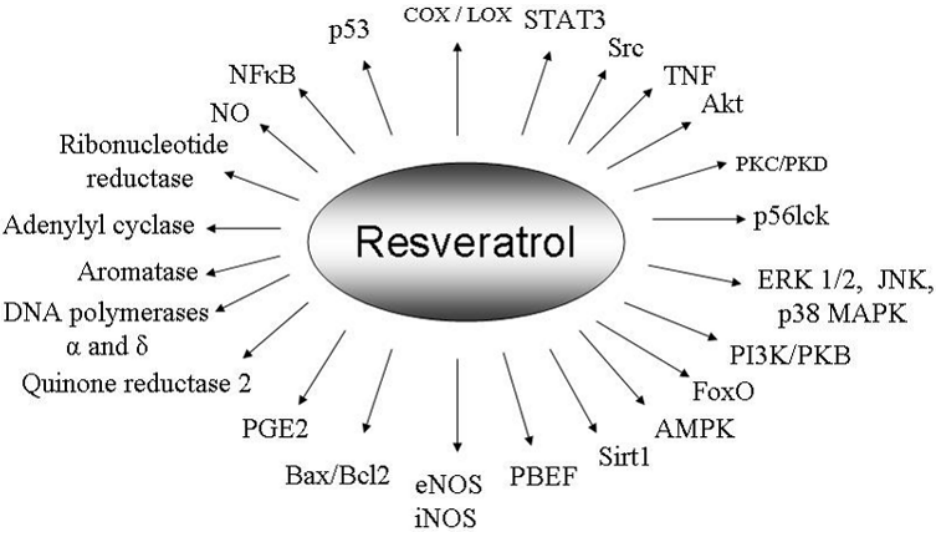

FIGURE 2. Molecular Targets of Resveratrol: as a pharmacological agent, resveratrol has wide spectrum of targets.

[10-40 mM] (Frémont *et al.* 1999; Bhat and Pezzuto 2001; Dong and Ren 2004; Aggarwal *et al.* 2004; Lee and Lee 2006). In contrast resveratrol protects hearts in a relatively low dose [5-20 μM] (Penumathsa and Maulik 2009; Xi *et al.* 2009; Das *et al.* 2006a; Kaga *et al.* 2005). This would tend to indicate that resveratrol provides diverse health benefits in a dose-response manner. In this section, we will discuss the importance of such dose dependency of resveratrol in providing health protection. There are quite a few studies to describe the dose dependency of resveratrol towards health benefit.

Wilson et al. (1996) showed that high dose [1 mg/kg] of resveratrol promotes atherosclerosis in case of hypercholesterolemic rabbits. They showed that resveratrol treatment did not adversely affect rabbit health other than promoting atherosclerosis. Both control and high dose [1 mg/kg] of resveratrol-treated groups showed similar body weight, food consumption, liver weight, serum chemistry profile or serum enzyme activities, lipoprotein concentration and LDL oxidation. In contrast to the anti-atherosclerotic effect for resveratrol, this study suggested that oral administration of high dose [1mg/kg] of resveratrol to hypercholesterolemic rabbits promotes atherosclerosis independent of difference in gross animal health, liver disease, lipoprotein cholesterol concentration (Wilson *et al.* 1996). In a study by Crowell *et al.* (2004), resveratrol [3000 mg/kg] caused renal toxicity when used in high concentration. Renal tubule dilatation, papillary necrosis, acute pelvic inflammation and increased incidence and severity of nephropathy were seen in the animals treated with high dose of resveratrol. Oral administration of high dose (3000 mg/kg bw/day) of resveratrol to the rats for 28 days resulted in

nephrotoxicity observed as elevated blood urea nitrogen (BUN) and creatinine level, increased kidney weights, gross renal pathology changes and an increased incidence and severity of histopathological changes in the kidneys. Low dose of resveratrol [300 µg/kg] did not result in nephrotoxicity. Animals treated with high dose also showed higher serum alanine aminotransferase (ALT) and alkaline phosphatase levels, significant lower hemoglobin concentration and lower red blood cell counts. High dose [3000 mg/kg] of resveratrol treated rats also showed reduction in weight of heart, lung/bronchi than those of the low dose resveratrol treated group (Crowell *et al.* 2004). The above study suggests that resveratrol causes renal toxicity when administrated in high dose. One study from France shows that at higher dose (60 µM), resveratrol inhibits the growth and induces apoptosis in case of both normal (60 µM) and leukemic (5-43 µM) hematopoietic cells (Ferry-Dumazet *et al.* 2002). In this study, the authors have shown that resveratrol induced a dose dependent decrease in cell number and cell proliferation by inducing apoptosis via activation of caspase cascade. Thus, resveratrol can be considered as an inhibitor for the human myeloid of lymphoid leukemic cell growth at high dose (43 µM). Resveratrol can reduce cell growth and induce apoptosis in case of normal cell when administered in high dose (60 µM) (Ferry-Dumazet *et al.* 2002). Thus, resveratrol has biphasic effects over low to high spectrum of concentrations. At low concentration (5 (M), resveratrol appears to increase cell proliferation, whereas apoptosis is induced in various cancer cells at 15 (M or higher concentration. It was also reported that resveratrol activates extracellular signal regulated kinase (ERK), a member of the mitogen-activated protein kinase (MAPK) family and stimulates endothelial nitric oxide synthase (eNOS) at low concentration (50 nM) in endothelial cell (Klinge *et al.* 2005). In a recent study from Korea, the authors have shown that resveratrol induced apoptosis in endothelial cells with increasing concentration (2.5-100 µM) (Kyungmin and Park 2006). This clearly indicates that resveratrol at a high dose/concentration has a strong pro–apoptotic effect on endothelial cells. In contrast, resveratrol inhibits oxidized LDL- induced cytotoxicity when used in low concentration (Ou *et al.* 2006). In case of human cancer cells (HT29, SW-620, HT-1080) and endothelial cells, resveratrol enhances proliferation when used at low dose (0.1-1 (g/ml) and induces apoptosis and decreases mitotic activity when used at high dose (10-100 (g/ml) (Szende *et al.* 2000). Cell numbers of human umbilical vein endothelial cells (HUVEC) cells in culture were shown to be decreased drastically at 10 (g /ml and 100 (g/ml concentration of resveratrol treatment. Szende et al (2000) showed that 1 (g/ml of resveratrol exerted a slight anti-proliferative effect but when resveratrol was used in a very small concentration (0.1 (g/ml) proliferation was stimulated. Kyungmin and Park (2006) showed that 100 (M resveratrol induced apoptosis by

cleavage of caspase 3. They have also shown that resveratrol has an inhibitory effect on cell migration. It is known that resveratrol induces the activation of ERK and reduces the activation of JNK when used in low dose (Klinge *et al.* 2005). In contrast, high dose of resveratrol stimulates JNK activity in variety of cancer cells (She *et al.* 2002). In the same study, Kyungmin and Park (2006) have shown that 100 (M resveratrol treatment declines the basal levels of Akt and eNOS phosphorylation in endothelial cell, indicating that resveratrol induces endothelial cell apoptosis and inhibits endothelial migration at a high dose. It is known that resveratrol can induce the activation of Akt and eNOS when used in low concentration (Dudley *et al.* 2008a). In another study with androgen–sensitive prostate cancer cells, resveratrol showed a proliferative activity at a low dose (5 (M), whereas it had a pro-apoptotic activity at a high dose (15 (M or higher) (Signorelli and Ghidoni 2005). One group from Italy showed the effect of resveratrol on some activities of isolated and in whole blood human neutrophils. In this study, the authors have shown that in volunteers with normal low basal O_2^- production resveratrol showed an inhibitory activity only at high concentrations (10^{-2} mg/ml). In case of volunteers with natural high basal O_2^- production, resveratrol inhibited superoxide anion generation at all concentrations (both in low and high concentration) (Cavallaro *et al.* 2003). In another study, Acquaviva et al. (2002) have shown that free radical-scavenging capacity of resveratrol depends on concentration. They have shown that antioxidant properties of resveratrol is increased with increasing concentrations of resveratrol, which was monitored by measuring the free radical–scavenging capacity of resveratrol with different concentration of resveratrol. It is known that in human esophageal carcinoma cells, resveratrol induces apoptosis when used in high concentration (100 mM/lit) and this high dose of resveratrol also downregulated Bcl2 protein expression and upregulated Bax protein expression in EC-9706 cells (Zhou *et al.* 2003). Mnjoyan and Fujise (2003) investigated the role of resveratrol in cell cycle progression and apoptosis of vascular smooth muscle cells (VSMCs). They have shown that resveratrol inhibited the growth of human aortic VSMCs at low concentrations (1 (M). That was due to the profound dose-dependent inhibition of DNA synthesis by resveratrol. This study has shown that resveratrol caused a dose-dependent increase in intracellular p53 and $p21^{WAF1/CIP1}$ levels. When used at lower concentrations (6.25–12.5 (M), resveratrol effectively blocked cell cycle progression of serum-stimulated VSMCs without inducing apoptosis, while at higher concentrations, resveratrol (25 (M) selectively induced apoptosis in the same VSMCs. Intriguingly however, the same high concentration of resveratrol could not induce apoptosis in quiescent VSMCs (Mnjoyan and Fujise 2003). Recently, Caddeo et al. (2008) showed that the effect of resveratrol on the cell proliferation, cell viability of HEK 293 cell before and after UV-B irra-

diation is dose dependent. When the cells were incubated with 10 (M resveratrol, it activated the metabolic activity of the cells, but in case of 50 (M resveratrol dose, a slightly deteriorative effect was observed and when the cells were incubated with 100 (M resveratrol, the metabolic activity was completely inhibited. They have also shown that resveratrol could protect cells from UV-B radiation much better when used in lower dose. In case of UV radiated HEK cells, it was shown that 100 (M resveratrol suppressed cell proliferation, whereas in case of 10 (M resveratrol treatment, the cell proliferation was higher (Caddeo *et al.* 2008). This study indicates that resveratrol is much more photoprotective when used in low dose. In an another study, Howitz et al. (2003) showed that the photoprotective effect of resveratrol from radiation induced apoptosis in HEK 293 cells was reversed at concentrations greater than 50 (M. Caddeo et al. (2008) also showed that at low concentration, resveratrol increased the number of cells without any evidence of toxicity. In contrast, cells treated with higher concentration of resveratrol showed loss of membrane integrity due to polymerized actin degradation and impaired functional status of cell (Caddeo *et al.* 2008).

Limited data exist regarding the adverse effects of resveratrol in aging. Juan *et al.* (2002) have shown that in rats, oral administration of 20 mg/kg resveratrol for 28 days produced no harmful effects as assessed by growth, hematology, clinical chemistry, and histopathology. In contrast, higher amounts of resveratrol (1000, and 3000 mg daily for 28 days) were shown to cause kidney damage (Crowell *et al.* 2004). Consumption of resveratrol at a modest dose results in an increase in the life span in case of 1 year old mice. However, when mice consumed larger doses (1800 mg/kg) of resveratrol, animals were shown to die within 3–4 months (Pearson *et al.* 2008).

As we discussed in previous section, several studies have shown that resveratrol possess biphasic function depending on dose. The cardioprotective properties of resveratrol also appear to be dose-dependent. At lower dose of 5 μM, resveratrol functions as an antioxidant, while at higher dose it may function as a pro-oxidant (Dudley *et al.*, 2008a). Our previous studies regarding cardioprotection of resveratrol showed that in low doses (5-10 μM), resveratrol functions as a cardioprotective agent (Penumathsa and Maulik 2009; Xi *et al.* 2009; Das *et al.* 2006b; Kaga *et al.* 2005). Red wines and white wines that contain resveratrol also possess cardioprotective properties at low to moderate doses (10-15 μM) (Sato *et al.* 2004, Dudley *et al.* 2008b). At low concentration, resveratrol (<10 (M) can protect the heart from ischemia/reperfusion related injury by making the heart pharmacologically preconditioned in a NO-dependent manner (Hattori *et al.* 2002), which was further confirmed by a subsequent study, which showed that the same concentration of resveratrol could not protect the heart from ischemia/reperfusion induced injury in case of iNOS knockout mice

(Imamura *et al.* 2002). It has been shown that 10 (M resveratrol could protect the heart by activating the survival signal through PI3-Kinase- Akt- Bcl2 signaling pathway (Das *et al.*, 2005b) and through adenosine A(3) receptor signaling, which accelerates the CREB phosphorylation through both Akt-dependent and -independent pathways (Das *et al.* 2005b). In related studies, low doses of resveratrol (e.g., 10 (M or 2.5 mg/kg) protected the mammalian hearts from ischemia/reperfusion injury by activating the phase II enzymes, HO-1 and Trx-1 and by Map Kinase signaling (Das *et al.* 2006b; Das *et al.* 2006c). In a related study, it was shown that 2.5 mg/kg resveratrol alleviated cardiac dysfunction in streptozotocin-induced diabetes by upregulating NO, thioredoxin, and heme oxygenase and MnSOD activity (Thirunavukkarasu *et al.* 2007). A specially designed study to determine the optimal concentration of resveratrol where the authors showed that there were no effects on ventricular function at 3.7 and 7.4 (M resveratrol, nor did any effect on myocardial infarct size. The maximum beneficial effect of resveratrol was noticed at 10 (M resveratrol. The higher dose (25 (M) of resveratrol still exerts cardioprotective effects, but the effects tend to be slightly reduced (Das *et al*, 2006c). In a more recent study, we randomly assigned the rats in five groups: control group (vehicle treated), low dose groups (treated with 2.5 mg/kg and 5.0 mg/kg resveratrol) and high dose groups (treated with 25 mg/kg and 50 mg/kg resveratrol). All rats were gavaged with either vehicle or different doses of resveratrol for 14 days. After 14 days of gavaging all rats were sacrificed and isolated hearts were perfused by working heart method in a working heart apparatus. All the hearts were subjected to 30 min ischemia followed by 2h reperfusion to examine the effects of different doses of resveratrol in ischemia/reperfusion induced cardiac injury. We have shown in this paper (Dudley *et al.* 2008a) that post ischemic cardiac functional parameters were improved by resveratrol treatment only at low doses (2.5 and 5 mg/kg). High dose resveratrol (25 and 50 mg/kg) significantly reduced the recovery of functional parameters like aortic flow, LVDP (left ventricular developed pressure), and LVdp/dt (First Derivative of Left Ventricular Developed Pressure). Cardiomyocyte apoptosis and myocardial infarction due to ischemia/reperfusion injury were reduced only in the low doses of resveratrol treatment, but not with high doses resveratrol treatment. As resveratrol is a well known antioxidant, we determined the effects of different doses of resveratrol on regulation of mRNA transcripts of some redox proteins, which were directly related to cardioprotection, like Trx-1, Trx-2, Grx-1 and Grx-2. These redox proteins play crucial role to maintain the redox homeostasis in mammalian system. Our result showed that ischemia/reperfusion reduced the level of mRNA transcript of these redox proteins due to oxidative stress and low dose resveratrol could prevent this reduction, whereas high dose resveratrol was unable to protect the reduction of redox protein mRNA transcript. Redox effector factor-1 (Ref-1) is

an important enzyme ubiquitously present in the mammalian system. Ref-1 plays a major role in DNA base excision repair pathway (Evans *et al.* 2000; Wilson and Barsky 2001)[2] D.M. Wilson III and D. Barsky, The major human abasic endonuclease: formation, consequences, and repair of abasic sites in DNA, *Mutat. Res.* 485 (2001), pp. 283–307. Article | PDF (720 K) | View Record in Scopus | Cited By in Scopus (113) It also serves as a transcriptional coactivator by stimulating the DNA binding activity of redox-sensitive transcription factors such as AP-1, nuclear factor _B (NF_B), p53, and cAMP response element binding protein (Xanthoudakis and Curran 1992; Huang and Adamson 1993). Consistently, Ref-1 enhanced Nrf2 binding to the ARE (Iwasaki *et al.* 2006), which in turn regulated the expression of a variety of enzyme proteins (Chan 2000). A recent study showed that ischemia/reperfusion could potentiate a rapid translocation of thioredoxin-1 into the nucleus which then interacts with Ref-1, leading to the generation of a survival signal (Malik *et al.* 2006). The same author also showed that Ref-1 induced a survival signal in ischemic heart via protein- protein interaction between NF_B, Ref-1, Trx-1 and Nrf2. (Gurusamy *et al.* 2007) Based on these studies we determined whether different doses of resveratrol could have diverse effects on Ref-1 profile in ischemic/reperfused heart. We have shown that ischemia/reperfusion downregulated Ref-1 level, but resveratrol could induce Ref-1 expression, only at a low dose. High dose resveratrol could not prevent the down-regulation of Ref-1 during ischemia/reperfusion injury (Figure 3. Data taken from Dudley et al. 2008a). The above study suggested that low dose resveratrol activated Ref-1 in ischemic heart and triggered Nrf-2 binding to ARE region and upregulated the expression of redox proteins like Trx and Grx. Upon ischemic stress, these redox proteins translocate into nucleus and bind with Ref-1, leading to activation of a survival signal to protect the heart. At low dose, resveratrol treatment can activate the survival signal by inducing Akt phosphorylation, which in turn activates Bcl2 and triggers cardiac cell survival whereas the reverse is true for the high dose of resveratrol (Figure 4. Data reproduced from Dudley *et al.* 2008a). Thus resveratrol appears to be dose-dependent in providing cardioprotection. Table 2 shows the effects of low and high doses of resveratrol on health benefits. The precise reason for generation of death signal at higher resveratrol dose is not clear. It is speculated that differential redox cycling of resveratrol between high and low dose might be responsible for survival and death signal. Resveratrol contains two phenol groups in it. A study by Boyer et al. (1988) showed that phenol reduces Fe^{3+} to Fe^{2+}. Iron plays a crucial role in free radical reactions leading to iron–oxygen complexes that remove hydrogen atoms from the polyunsaturated fatty acid membrane (Minotti and Aust 1989; Sotomatsu *et al.*, 1990; Rice-Evans and Burdon 1993). Miura *et al.* (2000) found that resveratrol possesses both antioxidant and pro-oxidant effects. Resveratrol promoted the reduction of Fe^{3+} by increasing the formation of

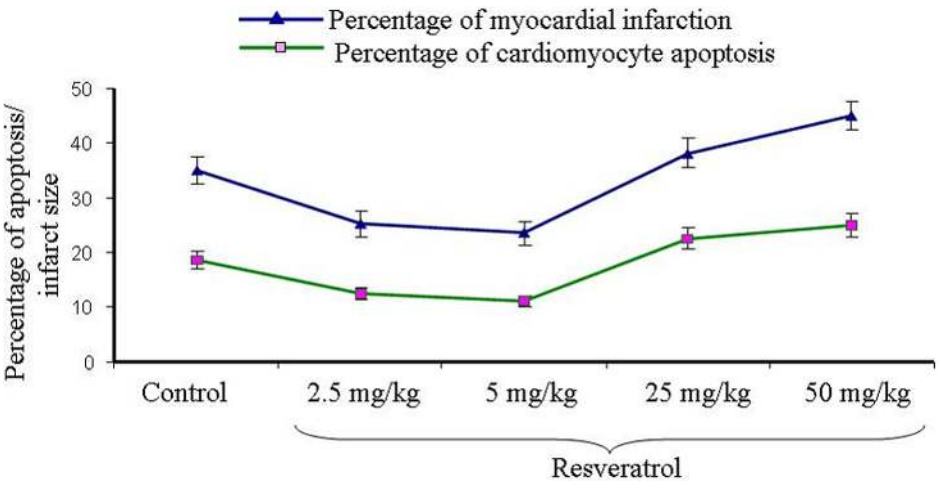

FIGURE 3. Effects of high and low doses of resveratrol on the myocardial infarct size and cardiomyocyte apoptosis (Graphs are re-plotted from Dudley *et al.*, 2008a). Myocardial infarction and cardiomyocyte apoptosis were measured by TTC method and TUNEL method respectively.

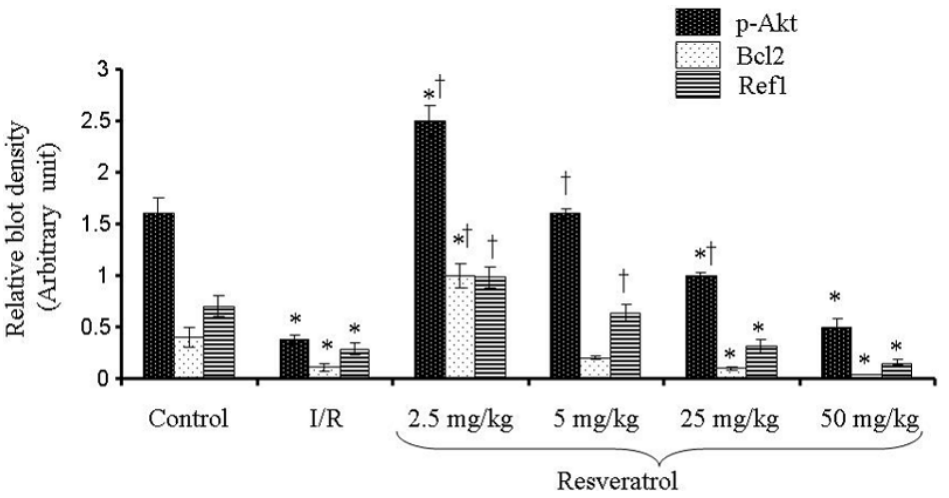

FIGURE 4. Effects of low and high doses of resveratrol on the expression of some survival pathway members like Akt, Bcl2 and Ref-1 (Graphs are re-plotted from Dudley *et al.*, 2008b). Expression of different proteins was measured by western blot technique. $^{*}p < 0.05$ vs. control; $^{\dagger}p < 0.05$ vs. I/R.

hydroxyl radicals through the Fenton reaction producing hydroxyl radicals and iron species (Yamazaki and Piette 1990). At higher doses, resveratrol causes DNA strand breakage by the accumulation of reduced ADP-Fe^{3+} in the presence of hydrogen peroxide. Fukuhara and Miyata (1998) found that resveratrol could bind to DNA and promoted DNA plasmid cleavage

TABLE 2: Effects of Low and High Doses of Resveratrol on Health Benefits.

Does of resveratrol used	Effects of resveratrol in health benefits	References
50 nM	Induces eNOS activity and activates ERK.	Klinge at al. 2005
0.15/0.25 □M	Inhibits collagen- induced platelet activation, phosphoinositide breakdown and protein kinase C activation.	Shen et al. 2007
5 □M	Increases cell proliferation. Inhibits oxidized LDL- induced cytotoxicity in HUVEC cells. Increases cell proliferation in androgen sensitive prostate cancer cells.	Jang et al. 1997, Ou et al. 2006, Signorelli and Ghidoni 2005
6.25-12.5 □M	Blocked cell cycle progression of serum-stimulated VSMC without inducing apoptosis.	Mnjoyan and Fujise 2003
10 □M	Activates metabolic activity and proliferation in HEK 293 cells. Improves cardiac functions after ischemia/ reperfusion injury. Protects the heart from I/R related injury by making the heart pharmacologically preconditioned. Activates survival signal members like Akt Bcl-2 Activates phase II enzymes, HO-1, Trx-1, Map kinase signal.	Caddeo et al. 2008, Hattori et al. 2002, Das et al. 2005a, Das et al. 2006a
25 □M	Exerts lesser degree of cardioprotection.	Das et al. 2006b
1 mM	Inhibits breast cancer progression in both estrogen-positive and estrogen-negative breast cancer cells.	Su et al. 2007
1-10 mM	Induces HO-1 in primary neuronal cultures and aortic smooth muscle cells.	Juan et al. 2005, Zhuang et al. 2003
0.1-1 □g/ml	Enhances proliferation of human cancer cells and endothelial cells.	Szende et al. 2000
2.5 mg/kg bw	Increases longevity through induction of proteins like Sirt, FoxO, and PBEF. Induces the activation of Akt, eNOS. Activates phase II enzymes, HO-1, Trx-1, Map kinase signal. Alleviates cardiac dysfunction in streptozotocin-induced diabetes by up regulating nitric oxide, thioredoxin, HO-1, MnSOD activity.	Mukherjee et al. 2009, Dudley et al. 2008a, Das et al. 2006c, Thirunavukkarasu et al. 2007
2.5-5 mg/kg bw	Improves post ischemic cardiac functions. Increase LVDP, LV dp/dt Reduces myocardial infarction, cardiomyocytes apoptosis. Induces expression of redox gene like Trx-1,Trx-2, Grx-1, Grx-2 Increase the expression of Ref-1, Nrf2, NF_B, p53.	Dudley et al. 2008a Xanthoudakis and Curran 1992 Huang and Adamson 1993, Gurusamy et al. 2007
22.4 mg/kg bw	Extends the life span, in case of high-calorie diets induce mice, by overexpressing SIRT1.	Nisoli et al. 2005
>5-100 □M	Induces apoptosis in activated T-cells in experimental allergic encephalomyelitis- induced mice.	Singh et al. 2007
15 □M or more	Induces apoptosis in various cancer cells. Exhibits pro-apoptotic activity.	Jang et al. 1997, Signorelli and Ghidone 2005

cont.

TABLE 2: *continued.*

25 □M	Selectively induces apoptosis in the human aortic VSMCs.	Mnjoyan and Fujise 2003
25-100 □M	Inhibits cell growth and proliferation by inducing apoptosis in both leukemic hematopoietic cells.	Ferry-Dumazet et al. 2002
50 □M	Reduces the proliferation of human multiple myeloma.	Bhardwaj et al. 2007
50-100 □M	Inhibits metabolic activity and cell proliferation.	Caddeo et al. 2008
50 □M-400 □M	Shows a marked inhibitory potential on cancer cell proliferation in the presence of etoposide.	Hwang et al. 2007
100 □M	Induces apoptosis by cleavage of caspase 3, declines the basal levels of Akt and eNOS phosphorylation in endothelial cell.	Kyungmin and Park 2006
>20 mM	Reduces NF_B activation and inhibits HO-1 expression in neuronal cultures.	Juan et al. 2005
50 mM	Induces cell death in mouse xenograft models of human neuroblastoma (SH-SY5Y, NGP and SK-N-AS) cells.	van Ginkel et al. 2007
100 mM	Induces cell death in human colorectal cancer cells (DLD1and HT29 cells).	Trincheri et al. 2007
	Induces apoptosis, downregulates Bcl2 protein expression and upregulates Bax protein expression in human esophageal carcinoma cells (EC-9706 cells).	Zhou et al. 2003
10-100 ug/ml	Induces apoptosis and decreases mitotic activity in case of human cancer cells (HT29, SW-620, HT-1080) and endothelial cells.	Szende et al. 2000
1 mg/kg bw	Induces atherosclerosis in case of hypercholesterolemic rabbits.	Wilson et al. 1996
10 mg/kg bw	Reduces cancer progression.	Su et al. 2007
>25 mg/kg/bw	Unable to induce post ischemic cardiac functions after ischemia/reperfusion injury. Reduces LVDP, LV dp/dt.	Dudley et al. 2008b
	Unable to protect myocardial infarction, cardiomyocytes apoptosis.	
	Reduces expression of redox gene like Trx-1,Trx-2, Grx-1, Grx-2	
	Reduces the expression of Ref-1, Nrf2, NF_B.	
625 mg/kg bw	Reduces the progression of prostate cancer in transgenic adenocarcinoma prostate (TRAMP) mice.	Harper et al. 2007
3000 mg/kg bw	Induce renal toxicity.	Crowell et al. 2004

in presence of Cu^{2+} under aerobic conditions and neutral pH. Resveratrol also reduces Cu^{2+} to Cu^{+} in the presence of the reactive oxygen species.

CONCLUSION

There are numerous plant-derived natural components, vitamins and minerals whose daily allowance requirement are safe and promote good health when taken at a low dose. When the same substances are taken at a high dose, they become toxic and produce adverse effects to the cells at the subcellular levels. Similarly resveratrol is good for health but the health benefit of resveratrol is dose-dependent. Low doses resveratrol protect health from different types of diseases, while high doses resvera-

trol can be detrimental for health. However, high dose resveratrol may be required in pathological conditions such as destroying cancer cells.

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