Resveratrol and diabetic cardiac function: focus on recent *in vitro* and *in vivo* studies

Belma Turan · Erkan Tuncay · Guy Vassort

Summary Resveratrol, a natural phytoalexin found in wine has the potential to impact a variety of human diseases. Resveratrol like other polyphenols activates many of the same intracellular pathways as those activated by caloric restriction. It can quench reactive oxidative species, ROS and induce eNOS and iNOS expression. Resveratrol also can activate SIRT1, a NAD$^+$-dependent deacetylase, that leads an improved in mitochondrial function, and then this procedure turns to activate the transcription factor Nrf2 that coordinates expression of key antioxidant mechanisms by binding to the antioxidant response elements. Resveratrol provides cardioprotection by triggering preconditioning and inducing autophagy. It also presents chemical similarities with estrogen and was reported to activate both nuclear and extranuclear estrogen receptors. Resveratrol treatment alleviated diabetes-induced cardiovascular system disorders via different endogeneous signaling pathways including oxidative stress/antioxidant defense system, glucose/insulin metabolism, overexpression of iNOS/nitrotyrosine, and preconditioning. Resveratrol treatment significantly reduced the blood glucose level in STZ-treated type 1 diabetic animals through insulin-dependent and insulin-independent pathways. Resveratrol triggers some of the similar intracellular insulin signalling components in myocardium such as eNOS, AKT through the AMPK pathway, and plays an essential role in Glut-4 translocation and glucose uptake in STZ-induced diabetic myocardium. However, resveratrol can exhibit hormetic action expressing health benefits at lower doses whereas being detrimental at higher doses. It might also exert antidiabetic effects by activating SIRT1 directly in the brain. This review includes a summary of the role of resveratrol and diabetic cardiac function including a brief discussion on *in vitro* and *in vivo* studies as well as our original observations in diabetic rats.

Keywords Redox status · Red wine · Polyphenol · Cardiovascular disease · Cardioprotection

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Introduction

Resveratrol (trans-3,4′,-5-trihydroxystilebene; 3,4′,5-stilbe-netriol; trans-resveratrol; (E)-5-(p-hydroxystyryl) resorcinol; 5-[(E)-2-(4-hydroxyphenyl)-ethenyl] benzene-1,3-diol ; $C_{14}H_{12}O_3$) (Fig. 1A), a natural polyphenol, is a phytoallexin that in nature protects plants against infection by fungi, especially *Botrytis cinerea*. It is found in grapes skin, red wine, berries, japanese knotweed, peanuts, roots of rhubarb and other plants from trace amounts to mg/g while exposure of grapes to UV or prolonged cold storage resulted in a 2- to 10-fold accumulation (Shakibaei et al. 2009). Although these plants and their extracts have been used for various therapeutic purposes by ancient cultures, resveratrol itself was first described in 1940 as a phenolic component of the medicinal herb hellebore, *Veratrum grandiflorum*. Little attention was given to it until its ability to inhibit growth of cancer cells in culture was discovered (Baur & Sinclair 2006). In light of the well-publicized French-paradox in a population on a high fat diet (Renaud & de Lorgeril 1992), researchers have focused on studying the mechanisms of the protective effects of moderate wine consumption,

Fig. 1 Mechanisms of resveratrol mediated action in cardioprotection of diabetic samples. **a** Resveratrol ($C_{14}H_{12}O_3$; MW: 228.24) is a stilbenoid, a type of natural phenol found in the skin of red grapes and in other fruits. **b** Summary on how cardioprotection with resveratrol can be maintained. The major contribution to health from resveratrol appears to be directed toward limiting progression of heart disease and atherosclerosis from genes to organs. *See details in text*
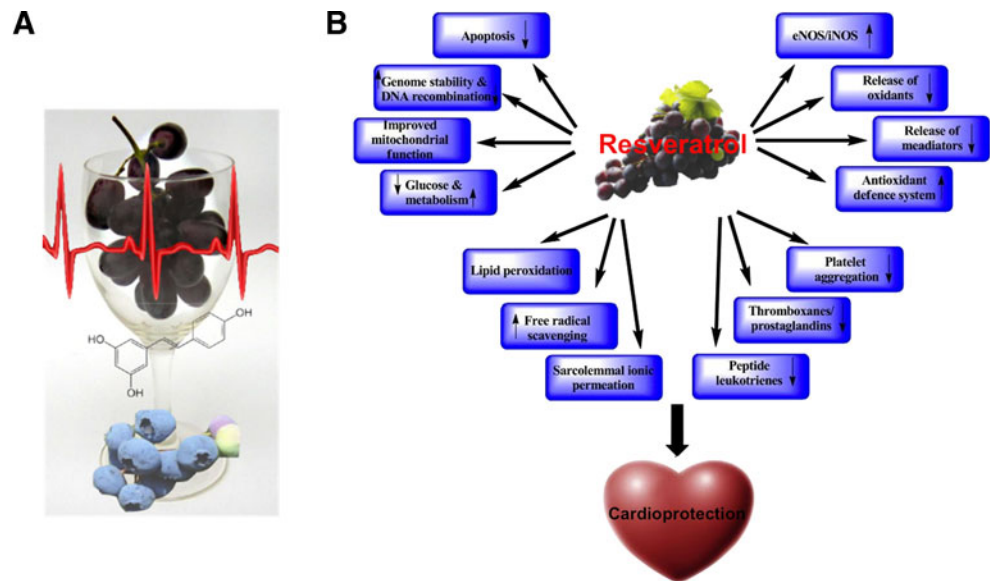
particularly on the cardiovascular system, after resveratrol presence in wine was reported in 1992 by Siemann and Creasy (Siemann & Creasy 1992). Resveratrol significantly extends the lifespan of the yeast *Saccharomyces cerevisiaen* (Howitz et al. 2003) as well as of a short-life fish *Nothobranchius furzeri* (Valenzano et al. 2006). However in upper Vertebrates, resveratrol does not affect lifespan of control mice while it clearly prevents most of the ill effects of a high fat diet in mice such as these that lived 30% longer, ie had the same lifespan as normal mice, even if the mice stayed fat and had high cholesterol. At the same time it improved insulin sensitivity and motor function (Baur et al. 2006; Lagouge et al. 2006) while it possesses an insulin-like effect with stimulating glucose uptake in STZ-induced diabetic rats (Su et al. 2006).

An increasing rate of preclinical evidence suggests resveratrol has the potential to impact a variety of human diseases. To translate encouraging experimental findings into human benefits, information is first needed on the safety and clinical efficacy of resveratrol. Published clinical trials have, as yet, largely focused on characterizing the pharmacokinetics and metabolism of resveratrol. Despite experimental advances in pathological cardiovascular system research, findings in humans are still quite limited. In recent years, diverse benefits to the renal (Sebai et al. 2008), nervous (Marambaud et al. 2005), antiinflammatory (Das & Das 2007) and cardiovascular systems have been described and reviewed (Baur et al. 2006; Centeno-Baez et al. 2011; Das & Das 2010; Dolinsky & Dyck 2011; Gresele et al. 2011; Markus & Morris 2008; Naderali et al. 2000; Petrovski et al. 2011; Robich et al. 2010; Wang et al. 2011; Vang et al. 2011; Wu & Hsieh 2011).

In line with the latest findings that are responsible for the increased recognition of resveratrol as a potential therapeutic and/or preventative agent, the aim of the present review

is to focus on recent experimental findings and clinical trials of resveratrol and other synthetic compounds with similar actions that could account for beneficial effects on the cardiovascular system of diabetic patients.

Role of resveratrol in the cardiovascular system: *in vitro* and *in vivo* studies

The biological activities of resveratrol may depend on its simultaneous activities on multiple molecular targets (Pirola & Frojdo 2008) as summarized in Fig. 2. Resveratrol like other polyphenols activate many of the same intracellular
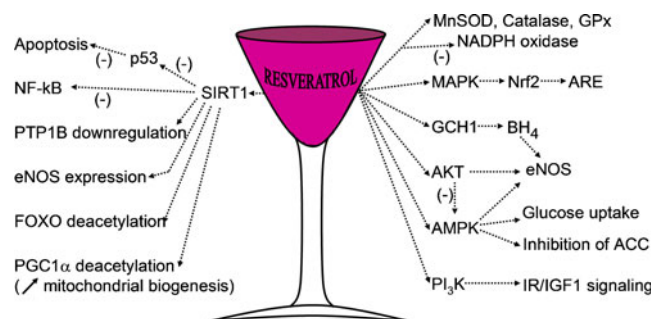

Fig. 2 General subcellular mechanisms involved in the resveratrol-induced effects. Abbreviations in use are: ACC: acetyl-CoA carboxylase; AKT: protein kinase B; AMP: adenosine monophosphate; AMPK: AMP kinase; ARE: antioxidant response element; eNOS: essential nitric oxide synthase; IR/IGF1: insulin receptor/insulin-like growth factor 1; GPx: glutathione peroxidase; MAPK: mitogen-activated protein kinase; NADPH oxidase: nicotinamide adenine dinucleotide phosphate-oxidase; NF-kB: nuclear factor-KappaB; Nrf2: nuclear factor (erythroid-derived 2)-like 2; PGC1α: peroxisome proliferator-activated receptor-γ (PPAR-γ) co-activator 1α; PI3K: phosphatidylinositol 3-kinase; PTB1B: protein tyrosine phosphatase 1B; p53: tumor protein 53; SIRT1: sirtuin (silent mating type information regulation 2 homolog) 1; SOD: superoxide dismutase

pathways as those activated by caloric restriction, well-known to improve health and longevity in animals but fail to mimic other aspects such as slowing heart rate or expending lifespan in nonobese animals (Dolinsky & Dyck 2011; Barger et al. 2008; Pearson et al. 2008). A unique miRNA footprint is present in the heart treated with resveratrol (Mukhopadhyay et al. 2010).

Anti-oxidative properties and NOS activation The anti-oxidative property of resveratrol is an important aspect of its physiological activity. Bioctive phenol, such as resveratrol can quenche reactive oxidative species, ROS such as hydrogen peroxide, superoxide and the hydroxyl radical, and thus avoid pro-oxidative damages (Kovacic & Somanathan 2010). Evidence has accumulated that ROS are important in the regulation of the transduction of signals by modulating protein activity via redox chemistry. Resveratrol increases the activity of SOD, catalase and GPx in cardiac H9C2 cells (Cao & Li 2004), SOD in aortic smooth muscle (Li et al. 2006) and SOD1 in endothelial cells (Spanier et al. 2009), although another study found no change in SOD1 and SOD2 in rat aortic segments *ex vivo*-treated with resveratrol (Ungvari et al. 2007). Thus, the resveratrol-induced protection of cardiomyocytes from injury in an episode of ischemy-reperfusion was attributed, in part, to reduced superoxide levels via its anti-oxidative properties (Goh et al. 2007). Also, resveratrol significantly reduced oxidative stress, one of the main causes of development of pathological cardiac hypertrophy in SHR (Alvarez et al. 2008). This is consistent with a recovery in the total antioxidant levels in SHR that allows to suggest alleviation of the oxidative stress may be one of the mechanisms by which resveratrol prevents the development of pathological hypertrophy and cardiac dysfunction in SHR (Thandapilly et al. 2010). In the two-kidney, one-clip hypertension rat model, resveratrol improved cardiovascular function through the augmentation of endogenous antioxidants and the inhibition of lipid peroxidation by maintaining a balance in oxidant/antioxidant status, and so ameliorates hypertension-induced oxidative injury in all tissues, including the cardiac one (Toklu et al. 2010). Resveratrol protects ROS-induced cell death by activating the AMP-activated protein kinase, AMPK in the H9c2 cardiac muscle cell line (Hwang et al. 2008). AMPK is a metabolic fuel gauge. Activation of AMPK acts to maintain cellular energy stores, switching on catabolic pathways that produce ATP, mostly by enhancing oxidative metabolism and mitochondrial biogenesis. Moreover AMPK enhances SIRT1 activity by increasing cellular NAD^+ levels, thus accounting for many of the convergent biological effects of AMPK and SIRT1 on energy metabolism (Canto et al. 2009). Resveratrol stimulates AMPK phosphorylation and activity, and consequently acetyl CoA carboxylase phosphorylation,

leading to downregulated lipid biosynthesis and upregulated fatty acid oxidation (Zang et al. 2006).

Several reports indicated that resveratrol can induce eNOS and iNOS expression (Hsieh et al. 1999; Imamura et al. 2002; Wallerath et al. 2002). Resveratrol is reported to up-regulate the expression of eNOS in mouse aorta (Wallerath et al. 2002; Leikert et al. 2002) and to down-regulate the expression of NAD(P)H oxidase, NOX4, an enzyme involved in the production of ROS, in human umbilical vein endothelial cells (HUVEC) (Spanier et al. 2009). That suggests the improvement of vascular function generated by resveratrol may be related to the increase in NO formation and the decrease of ROS. Beneficial role of resveratrol via triggering NO-dependent signalling in cardiovascular system is further demonstrated by *in vivo* animal studies after resveratrol supplementation. There is an overexpression of iNOS and VEGF within 24 h of resveratrol treatment that further increases till 7 days. The isolated working heart preparations from the later treated rats demonstrated that resveratrol provides cardioprotection as evidenced by superior post-ischemic ventricular recovery, reduced myocardial infarct size and decreased number of apoptotic cardiomyocytes, as well as enhanced expressions of iNOS, eNOS and VEGF (Das et al. 2005a).

Sirtuins Another prevailing hypothesis in comparing caloric restriction and resveratrol is that both activate SIRT1, a NAD^+-dependent deacetylase. The activity of SIRT1 is directed to histone proteins as well as to several transcription factors including p53, the FOXO-family and the metabolic regulator and transcriptional coactivator, peroxisome proliferator-activated receptor-γ (PPAR-γ) co-activator 1α, PGC-1α. By doing so it improves mitochondrial function, induces genes for mitochondrial and fatty acid oxidation and increases mitochondrial membrane potential (Lagouge et al. 2006; Gerhart-Hines et al. 2007). Resveratrol, by inducing the expression of several genes including SIRT1, SIRT2, SIRT4, FoxO1, FoxO3a, prevents aging-related decline in cardiovascular function including cholesterol level and inflammatory response. PGC-1α also induces the expression of the insulin-sensitive glucose transporter Glut-4 gene and increases glucose uptake (Michael et al. 2001). SIRT1 levels were also dose-dependently increased in resveratrol-treated human endothelium cells while resveratrol inhibited their senescent phenotype on H_2O_2-treatment (Kao et al. 2010). On testing the production of hyperglycemia-induced mitochondrial ROS in cultured human coronary arterial endothelial cells, it is shown that resveratrol upregulated MnSOD expression and increased cellular GSH content in a concentration-dependent manner while these effects were attenuated by SIRT1 knockdown and mimicked by Sirt1 overexpression (Ungvari et al. 2009). Resveratrol attenuates doxorubicin-induced cardiomyocyte apoptosis in mice

through SIRT1-mediated deacetylation of p53 (Zhang et al. 2011). However, microarray analysis of global gene expression profiles in the heart suggests that many of the cardiovascular benefits of caloric restriction are achieved by a lower dose of resveratrol that is necessary to activate SIRT1, and the concept that resveratrol is a direct activator of SIRT1 was challenged (Dolinsky & Dyck 2011; Pacholec et al. 2010). Furthermore resveratrol, at the same concentration range at which it activates sirtuins, has a major influence on the IR/IGF-1 controlling pathway by acting as a competitive inhibitor of class 1A PI3K and leading to improved insulin sensitivity (Frojdo et al. 2007).

Transcription factor Nrf2 There is increasing evidence that activation of nuclear factor (erythroid-derived 2)-related factor-2, Nrf2 is another important mechanism by which resveratrol exerts cytoprotective effects. Nrf2 coordinates expression of key antioxidant mechanisms by binding to the antioxidant response elements, ARE in the regions of target genes including NAD(P)H:quinine oxidoreductase 1, NQO1 and heme oxygenase-1, HO1 which regulates mitochondrial and cellular levels of ROS (He et al. 2006). Resveratrol, in human coronary arterial endothelial cells, increases the transcriptional activity of Nrf2 and up-regulates several ARE-regulated genes involved in free radical metabolism in an Nrf2 dependent manner (Ungvari et al. 2010). It has also been recently demonstrated that resveratrol, after rat gavage or directly applied on the rat cardiac stem cells, significantly enhances expression of Nrf2 improves cell survival and cardiac functional parameters (Gorbunov et al. 2011; Gurusamy et al. 2010).

Preconditioning and autophagy Other mechanisms in which resveratrol is involved include autophagy and preconditioning. As summarized in Fig. 1B, literature data have shown that at low doses, resveratrol acts to provide health benefits to humans as an anti-apoptotic agent, providing cardioprotection as evidenced by increased expression in cell survival proteins, improved postischemic ventricular recovery and reduction of myocardial infarct size (Das et al. 2005a; Bradamante et al. 2003; Das et al. 1999; El-Mowafy & White 1999; Fremont et al. 1999; Hung et al. 2000; Hung et al. 2004; Kiziltepe et al. 2004). Resveratrol is known to protect the heart from ischemia-reperfusion injury (Das et al. 1999; Hung et al. 2004; Ray et al. 1999) as well as to trigger preconditioning in the heart (Petrovski et al. 2011; Imamura et al. 2002; Das et al. 2005b; Hattori et al. 2002). The adenosine A1 receptor, multiple kinases, including protein kinase C (PKC), MAPKs, and tyrosine kinases, and the mitochondrial ATP-sensitive potassium (K-$_{ATP}$) channel are known regulatory pathways to play a crucial role in preconditioning-mediated cardioprotection (Parratt & Kane 1994; Tanno et al. 2000; Tsuchida et al. 2002). Thus,

inhibition of K-$_{ATP}$ channel blocks the effects of preconditioning and K-$_{ATP}$ channel openers can simulate ischemic preconditioning (Parratt & Kane 1994; Liu et al. 1998). It has been recently demonstrated that the cardiac K-$_{ATP}$ channel is directly regulated by AMPK activation, implying that during metabolic stress a small change in cellular AMP that activates AMPK could be a trigger of K-$_{ATP}$ channel opening (Yoshida et al. 2011). Similar to ischemic preconditioning, resveratrol uses mitogen-activated protein kinases, MAPKs as upstream signaling targets. The cardioprotection afforded by resveratrol was partially abolished with PD98059, SB-202190 and H89, respectively ERK1/2 and p38 MAPK and MSK-1 inhibitors while these kinases were phosphorylated by resveratrol implying they play roles in resveratrol-mediated preconditioning (Das et al. 2006).

Cardioprotection induced by ischemic preconditioning induces autophagy, another form of stress adaptation for degrading damaged or long-lived proteins, as a first line of protection against oxidative stress. Long-term resveratrol treatment exerted cardioprotection of ischemia in isolated perfused heart as evidenced by ventricular performance, infarct size and cardiomyocyte apoptosis (Lekli et al. 2506). Cardioprotection was reinforced by γ-tocotrienol while both compounds induced synergistically greater amount of survival signal through the activation of AKT Bcl2 survival pathway. Resveratrol-induced autophagy was confirmed in H9c2 cardiac myoblast cells at low doses (0.1–1 μM) that induces the expression of Rictor, a component of mTOR complex 2, and activates its downstream survival kinase AKT while autophagy was attenuated with the higher dose of resveratrol (Gurusamy et al. 2010). Moreover, rat supplementation with Longevinex, resveratrol added with quercetin and rice bran phytate, induced superior cardiac performance, reduced infarct size and enhanced expression of SIRTs that are correlated with induction of autophagy. In concert, Longevinex caused phosphorylation and nuclear translocation of FoxO1, FoxO3a, and FoxO4, indicating involvement of FoxOs with autophagy (Mukherjee et al. 2010). Recently, resveratrol, similarly to melatonin, both at concentrations found in red wine, was reported to significantly reduce infarct size in mouse hearts, but not in TNF receptor 2-knockout or STAT3-deficient mice, implying that resveratrol protects via the activation of the newly discovered survivor activating factor enhancement, SAFE prosurvival signaling pathway that involves the activation of tumor necrosis factor alpha, TNFα and the signal transducer and activator of transcription 3, STAT3 (Lamont et al. 2011).

Other resveratrol effects Some studies have shown that resveratrol blunted aortic banding-induced concentric hypertrophy and improved cardiovascular remodelling during hypertension (Juric et al. 2007). The amelioration of cardiovascular remodelling was attributed to the anti-inflammatory

and anti-fibrotic effects of resveratrol in DOCA-salt hypertensive rats (Chan et al. 2011). This amelioration in DOCA-salt rats may occur without lowering of blood pressure as it has been reported for the resveratrol-induced prevention of hypertrophy and cardiac dysfunction in young SHR (Thandapilly et al. 2010; Dolinsky et al. 2009).

Resveratrol is likely to exert potential cardioprotective actions through a variety of other mechanisms, including inhibition of endothelin-1 synthesis (Khan et al. 2002) and vasorelaxation (Naderali et al. 2000; Chen & Pace-Asciak 1996). In a recent *in vitro* study, Min et al. (Min et al. 2010) showed that resveratrol effectively attenuated the inhibition of lysoposphatidlcholine, LPC on both endothelium-derived relaxing factor and endothelium-derived hyperpolarizing factor in a concentration-dependent manner, as well as inhibited elevated K^+-induced vascular contracture without any effect on acetylcholine-induced endothelium-dependent relaxation in cultured rat aorta.

Estrogen-like effects Resveratrol presents chemical similarities with estrogen. The later mediates its effects on the cardiovascular system by activation of estrogen receptors, ER which can alter gene transcription in the nucleus or acutely activate kinase signaling in the cytosol. Resveratrol activates both nuclear and extranuclear ER. It rapidly activates MAPK signaling pathway, induces ER alpha-Cav-1-c-SRC interaction, resulting in eNOS phosphorylation and NO production by HUVEC (Klinge et al. 2005; Klinge et al. 2008). At concentrations (3–10 μM) comparable to those required for its biological effects, resveratrol inhibits the binding of estradiol to estrogen receptor, it also increases the expression of native estrogen-regulated genes (Gehm et al. 1997). Resveratrol also enhances eNOS expression via ER-independent SIRT1 activation (Csiszar et al. 2009). One mechanism by which estrogen improves both vascular health and reduces cardiomyocytes death is by activation of eNOS (Murphy 2011). Besides, BH4 is a cofactor for eNOS and in its absence eNOS becomes uncoupled and generates superoxide and little NO. BH4, rapidly oxidized by peroxinitrite, is reduced with aging and its lack of up-regulation during hyperglycemia prevents infarct-sparing effect of preconditioning (Amour et al. 2010). In apolipoprotein E-KO mice, resveratrol up-regulated SOD, catalase and glutathione peroxidise, down-regulated NADPH oxidases and in parallel enhanced the cardiac expression of GTP cyclohydrolase 1, the rate-limiting enzyme in BH_4 biosynthesis. Enhanced BH_4 synthesis and reduced BH_4 oxidation contribute to reverse eNOS uncoupling (Xia et al. 2010). The heart also expresses high levels of estrogen-related receptor α, ERRα that aids maintaining its high metabolic activity, and may regulate genes involved in contraction, Ca^{2+} homeostasis and ATP transport across membranes (Ranhotra 2010). ERRα, intimately interwining in a

feed-forward cycle with PGC-1α (Schilling & Kelly 2011), inhibits gluconeogenesis by down-regulating genes such as PEPCK suggesting its usefullness in the management of diabetes and hyperglycemia.

Basic cardiac mechanical and electrical activities of resveratrol Experimental findings provide evidence that resveratrol exerts multiple direct actions on cardiac myocytes which are not observed when it is applied to the animals. We studied the direct effects of resveratrol exposure on the mechanical and electrical activities of both right atrium and left ventricular papillary muscle strips isolated from the same rat (Buluc et al. 2007). The spontaneous contractile force of the right atrium was depressed by about 60% following 0.1 mM resveratrol exposure for 20 min, and by about 20% in the papillary mucle (Fig. 3A). Similarly, the intracellular action potential duration was affected with different grades in these two different heart preparations (Fig. 3B). We observed that exposure to the K-$_{ATP}$ channel blocker glyburide prevents significantly these resveratrol-induced changes. Previously, Liew *et al.* (Liew et al. 2005) and Zhao *et al.* (Zhao et al. 2004) studying the direct effects of resveratrol on heart preparations demonstrated that its acute application decreases Ca^{2+} transient amplitude and simultaneously increases cell shortening in half the cells tested while decreasing shortening in the other half, showing enhanced myofilament Ca^{2+} sensitivity. Also, action potential duration in heart preparations and peak L-type Ca^{2+} current, I_{CaL} in isolated cardiac myocytes were reduced in a dose- and time-dependent manner. In these works, application of the K^+-channel blocker tetraethylammonium chloride, or pretreatment with NG-nitro-L-arginine methyl ester, a NO synthase inhibitor, failed both to abolish the effects of resveratrol while cardiomyocyte incubation with an estrogen receptor antagonist suppressed them (Liew et al. 2005). Later works confirmed the resveratrol-induced inhibition of I_{CaL}, and increase in the sarcolemmal K-$_{ATP}$ current, I_{K-ATP} and further reported selective enhancement of Iks without an effect on Ikr, respectively the slow and rapid K^+ currents in guinea pig, or in rat, a reduction of Ito, Iss and I_{K1} respectively the transient outward, sustained and inward rectifying K^+ currents together with the sodium current, I_{Na} that could in all cases account for the resveratrol-antiarrhythmic effects (Chen et al. 2007; Chen et al. 2008; Zhang et al. 2006).

Role of resveratrol in diabetic cardiovascular disorders

Diabetes and obesity are evolving as two of the major diseases of the 21st century, with a significant increase in morbidity and mortality worldwide. As a result, there is an increasing need to identify potential therapeutic targets for
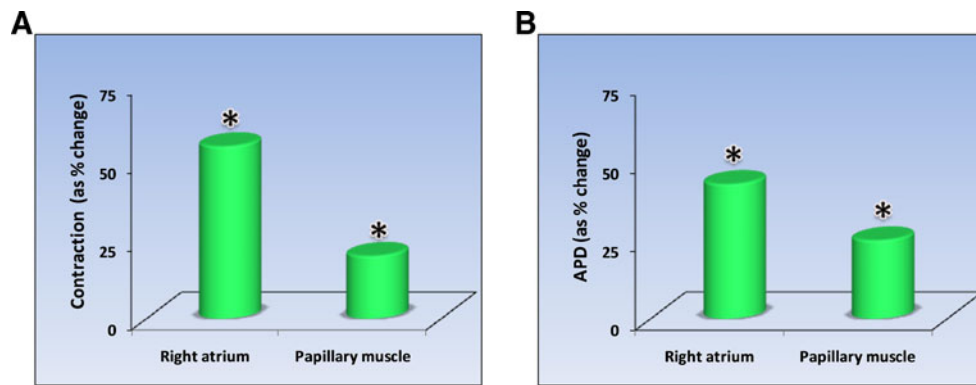
Fig. 3 Acute effect of resveratrol on mechanical and electrical functions of heart. Resveratrol (10^{-4} M) exposure to spontaneously beating right atrium isolated from 3-month old male rats induced a significant decrease in the basal contractile activity while similar doses of resveratrol application on to left papillary muscle strips (electrically stimulated by 3-ms duration rectangular pulses twice threshold at 0.1 Hz) induced a small decrease in contraction. **a** Mean (±SEM) responses (number of samples≥7 in each experimental protocol) to 10^{-4} M

resveratrol exposure in atrium and in papillary muscle are given as % change of their basal activitiy. **b** Inhibitory effects of resveratrol exposure (10^{-4} M) on action potential duration (APD) measured in atrial and papillary muscles. Action potential recording was performed using a glass microelectrode (10–15 MΩ; filled with 3-M KCl) under electrical stimulation and sampled at 10 kHz (adapted from (98)). *$p<0.01$ vs. initial value, student t-test

the management of these disorders. Diabetic cardiomyopathy has been associated with both type 1 (insulin-resistant) and type 2 (insulin-resistant) diabetes and is characterized by both early-onset diastolic and late-onset systolic dysfunctions (Rahangdale et al. 2009). Cardiac dysfunction occurring during type 1 and type 2 diabetes results from multiple parameters including glucotoxicity, lipotoxicity, fibrosis and mitochondrial uncoupling. However, type 2 diabetes carries additional risk factors compared to type 1, including insulin resistance, obesity and dyslipidemia. It is also a far more common health problem and it is a major risk factor for congestive heart failure.

Anti-oxidative properties and NOS activation It is a well-known fact that hyperglycemia increases the production of ROS, alters the cellular redox status and causes rapid changes in membrane function, followed by contractile dysfunction within weeks in the diabetic heart (Rahangdale et al. 2009; An & Rodrigues 2006; Ayaz et al. 2004; Ayaz & Turan 2006; Boudina & Abel 2007; Brownlee 2005; Ceriello 2003; Forstermann 2008; Pervaiz & Holme 2009; Xu et al. 2002).

Mitochondrial biogenesis occurs early in the development of diabetic dysfunction through a transcriptional regulatory circuit that involves activation of PGC-1 gene expression by the fatty acid-activated nuclear receptor PPARα (Duncan et al. 2007). PPARα is highly expressed in the heart and other tissues that rely primarily on fatty acid oxidation vs glucose utilisation. Insulin resistance and diabetes cause a shift of myocardial energy metabolism toward an increase reliance on fatty acids, in part driven by activation of PPARα (Finck et al. 2002). Forced PPARα overexpression decreases cardiac recovery after ischemia-

reperfusion, whereas lowering PPARα expression protects against ischemic damage (Sambandam et al. 2006). A recent work describes that a PPARα promoter variant impairs estrogen-related receptors, ERR-dependent transactivation and decreases mortality after acute coronary ischemia in patients with diabetes (Cresci et al. 2010).

In patients as well as in chemically-induced diabetic animals, there is a marked increase in the level of oxidative stress, which is a common pathway linking diverse mechanisms for the pathogenesis of diabetes due to hyperglycemia (Matkovics et al. 1997; Torres et al. 1999). Moreover, there is a close relationship between impaired insulin signalling and alteration in heart function via depressed endogenous antioxidant defense mechanism (An & Rodrigues 2006; Ayaz et al. 2004; Forstermann 2008). Resveratrol treatment alleviated diabetes-induced cardiovascular system disorders via different endogeneous signaling pathways including oxidative stress/antioxidant defence system, glucose/insulin metabolism, overexpression of iNOS/nitrotyrosine, and preconditioning. Resveratrol treatment significantly reduced the blood glucose level in STZ-treated type 1 diabetic animals through insulin-dependent and insulin-independent pathway (Alvarez et al. 2008; Chi et al. 2007; Huang et al. 2010). Homeostasis of blood glucose by insulin involves stimulation of glucose uptake by translocation of glucose transporter Glut-4 from an intracellular pool to the caveolar membrane system. Resveratrol increased GLUT-4 expression and reduced cardiac apoptosis in ischemic-reperfused hearts in the presence or absence of glucose intake in Zucker obese rats (Lekli et al. 2008). Resveratrol treatment also reversed the decreased association of Glut-4/Cav-3 and increased association of Cav-1/eNOS observed in diabetes. In fact, resveratrol triggers some of the similar intracellular

insulin signalling components in myocardium such as eNOS, AKT through the AMPK pathway, and particularly by regulating the caveolin-1 and caveolin-3 status resveratrol might play an essential role in Glut-4 translocation and glucose uptake in STZ-induced diabetic myocardium (Penumathsa et al. 2008). The overproduction of the free radical nitric oxide, NO by activated immunocompetent cells with subsequent development of local oxidative stress is supposed to be one of the possible pathophysiological mechanisms during chemically-induced diabetes. The blockade of increased NO production partially suppresses the hyperglycemia and the increase of glycated hemoglobin concentration (Thirunavukkarasu et al. 2007). Supporting these statements, Alnaeb et al. (Alnaeb et al. 2007) demonstrated that the number of endothelin-1, ET-1 receptors was significantly higher whereas, the expression of endothelial NO synthase, eNOS was significantly lower when comparing aortas from normal rabbits with these from diabetics ones. In rats, eNOS expression in aorta was significantly lower in insulin-resistant and diabetic rats compared with controls and the decrease was more pronounced in those of diabetic rats (Arrick et al. 2011). Resveratrol, by inhibiting oxidative/nitrative stress, improves particularly left ventricular diastolic relaxation (Zhang et al. 2010).

Sirtuins SIRT1-activating molecules such as resveratrol show significant therapeutic potential for the management of metabolic disorders. In diet-induced obesity, SIRT1 activation results in improved glucose tolerance, increased insulin secretion, and resistance (Banks et al. 2008; Bordone et al. 2007; Pfluger et al. 2008). The beneficial effects of resveratrol appear, in part, replicated by overexpression of SIRT1 (Bordone et al. 2007), or by treatment with SIRT1720, a structurally unrelated SIRT1 activator (Feige et al. 2008). A reduced enzymatic activity of SIRT1 contributes to SERCA2a repression in type 1 diabetes. Resveratrol, through activation of SIRT1, improves SERCA2a expression and cardiac function in diabetic mice. SIRT1 knockout mice are highly sensitive to diabetes-induced decline in SERCA2a mRNA. Additionally, SIRT1 acts as a transcriptional activator of SERCA2 gene expression of cardiomyocytes in high glucose conditions. (Sulaiman et al. 2010). In the aortas of type 2 diabetic db/db mice, resveratrol increases mitochondrial content in endothelial cells via activating SIRT1, and a pathway that involves the upregulation of eNOS. The expression of the mitochondrial biogenesis factors PGC-1α, Nrf-1, and Tfam in CAECs was significantly increased by resveratrol (Csiszar et al. 2009). Resveratrol exerts potent antidiabetic effects when delivered orally to animal models of type 2 diabetes. However since SIRT1 is expressed in the central nervous system it has been hypothesized that resveratrol antidiabetic effects are mediated by the brain. Indeed long-term intracerebroventricular

infusion of resveratrol normalizes hyperglycemia and greatly improves hyperinsulinemia in diet-induced obese and diabetic mice. This treatment also leads to reduced hepatic phosphoenolpyruvate carboxylase 1 mRNA and protein levels and ameliorates pyruvate-induced hyperglycemia (Ramadori et al. 2009). It was recently confirmed that mediobasal hypothalamic SIRT1 is essential for resveratrol effects on insulin action in rats (Knight et al. 2011). AMPK signaling known to regulate glucose production and transport, insulin release and preserved cardiac integrity is dysregulated in many disorders including diabetes (Dolinsky & Dyck 2006). AMPK phosphorylation is negatively correlated with the expression of phosphatases 2A and 2 C (PP2A and 2 C) (Wang & Unger 2005; Wu et al. 2007). Diabetes markedly decreased AMPK phosphorylation while contractile function is similarly impaired in AMPK kinase-dead mice. Resveratrol, like the protease inhibitor UCF-101, downregulates the AMPK degrading enzymes PP2A and 2 C and protects against the STZ-induced cardiac dysfunction (Li et al. 2009). In AMPK-deficient mice, resveratrol did not induce expression of genes important for mitochondrial biogenesis, in agreement with the fact that resveratrol did not increase the metabolic rate and reduce fat mass while it increased the NAD$^+$/NADH ratio which may explain how resveratrol may activate SIRT1 indirectly (Um et al. 2010). Also, the reduced phosphorylation of AKT and AMPK observed in STZ-induced type 1 diabetic rats was reversed by resveratrol (Penumathsa et al. 2008).

Transcription factor Nrf2 Nrf2 is a critical regulator of defense against ROS in both control and diabetic hearts by mediating the basal expression and induction of ARE-controlled cytoprotective genes. ROS production is significantly higher in Nrf2 KO mice and is further markedly more increased by a high concentration of glucose concomitantly with higher apoptosis (He et al. 2009). In the hearts of STZ-induced diabetic mice and diabetic patients Nrf2 expression significantly decreased along with significant increases in 3-nitrotyrosine accumulation and ERK phosphorylation (Tan et al. 2011). The protective nature of resveratrol, mediated by Nrf2, has also recently been reported in diabetic kidneys. Resveratrol treatment revealed a significant improvement in redox status with reduced glutathione levels, decline in lipid peroxides, hydroperoxides and protein carbonyls levels, and normalization of the renal expression of Nrf2/Keap1 and of its downstream regulatory proteins in the diabetic group of rats (Palsamy & Subramanian 2011). Such an Nrf2 dependent protective pathway of resveratrol remains to be confirmed in diabetic heart.

Preconditioning and autophagy During preconditioning, small doses of resveratrol can exert an adaptive stress

Table 1 General parameters of experimental rats

	Body weight (g)	Blood glucose (mg/dL)	Blood insulin (fmol/mL)	Serum MDA (μmol/mL)	Serum GSH/GSSG
CON ($n=20$)	248±6	104±4	300±19	132±9	70±3
DM ($n=12$)	197±8[*]	510±9[*]	120±18[*]	290±18*	21±5*
DM+RES ($n=10$)	226±6[*,†]	380±8[*,†]	198±12[*,†]	143±10	65±5

Three-month-old male Wistar rats, weighing 200–250 g, were subjected to single doses intraperitoneal injection of streptozotocin (STZ; 50 mg/kg, Sigma) (DM group). Age-matched control rats received an injection of citrate buffer alone (CON group). A blood glucose concentration>3-fold those of age-matched controls for 7 days and 4–5 weeks post-STZ injection was the criterion for experimental diabetes. Half of the diabetic rats following 7 days of STZ injection were treated with resveratrol (DM+RES group, 2 mg/kg body weight, daily for 4–5 weeks). n, number of rats. Values are given as mean ± SEM. *$p<0.05$ *vs.* CON group, and [†]$p<0.05$ *vs.* DM group, by ANOVA.

response, forcing the expression of cardioprotective genes and proteins such as heat shock and antioxidant proteins. It is long known that preconditioning is the most powerful technique known to promote cardioprotection under pathological conditions (Jennings et al. 1991). However cardioprotective effects of preconditioning are limited in the diabetic heart since chronic diabetes mellitus-associated deficit in survival pathways, impaired function of mito-K-$_{ATP}$ channels, MPTP opening and high oxidative stress playing key roles are paradoxically suppressed (Balakumar & Sharma 2011). The diabetic state rendered the animals more susceptible to myocardial I/R injury, and the mortality rate and inducible nitric oxide synthase (iNOS)/ nitrotyrosine protein expression and superoxide anion production are further increased in I/R-injured diabetic hearts. Pharmacological pretreatment with resveratrol alleviated cardiac dysfunction in diabetic rats subjected to I/R by significantly inducing activation of AKT/eNOS signalling, in addition to increased activation of MnSOD activity (Thirunavukkarasu et al. 2007). Resveratrol treatment reduced infarct size and apoptotic cell death for both

diabetic and control group rats, but the extent of infarct size and apoptosis remained higher for the diabetic group compared to the normal group. Many proteins related to energy metabolism, identified as mitochondrial proteins and oxidative stress and redox proteins in the diabetic group including Hsc70, HSPp6, GRP75, peroxiredoxin (Prdx)-1 and Prdx-3 were reversed (Thirunavukkarasu et al. 2007). Resveratrol also inhibited iNOS/nitrotyrosine protein overexpression and superoxide anion overproduction in I/R-injured diabetic (Huang et al. 2010). Furthermore, hyperglycemia, impairment of insulin signaling, overexpression of iNOS/nitrotyrosine, and superoxide anion overproduction were markedly rescued by the combination treatment of resveratrol and insulin; nevertheless, there was improvement in mortality rate (30%) or cardiac performance over resveratrol treatment alone (Huang et al. 2010).

Other resveratrol effects The vascular smooth muscle cell of the resveratrol-treated rats was characterized with less proliferation, lower NF-kappaB, and Erk1/2 activation. Altogether
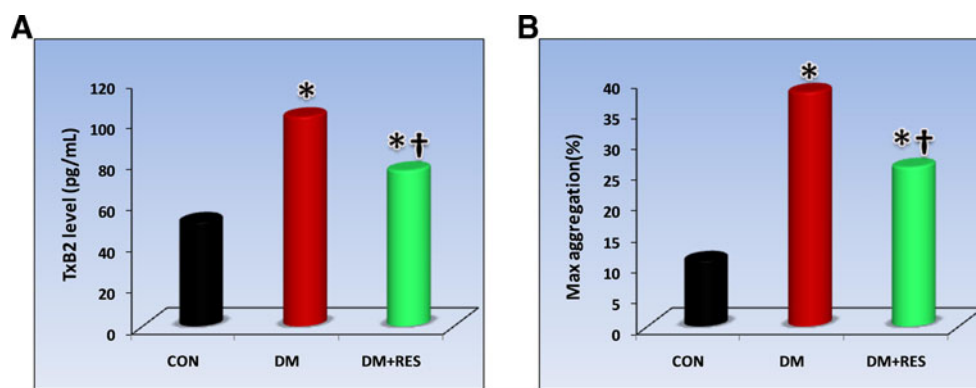

Fig. 4 Effects of resveratrol treatment on maximal amplitude of thrombin-induced platelet aggregation and thromboxane B2 (TxB2) level of diabetic rats. Diabetes was induced by intraperitoneal injection of streptozotocin (STZ) in 3-month old male Wistar rats as described previously (for methods see (Aydemir-Koksoy et al. 2010)) and a week after STZ injection, one group of the diabetic rats (DM group) was treated with 2 mg/kg body weight daily (orally) for 4 weeks (DM+RES group) while the second DM group was kept as the untreated DM group. A third group rats without STZ injection was kept as control rats (CON group). Thrombin-induced aggregation of the platelets was evaluated by optical technique (Ersoz et al. 2003). Thromboxane B2 (TxB2) was measured by enzyme-linked immunoassay in thrombin-induced platelets. Means (±SEM) TxB2 level and maximal platelet aggregation are given in **a** and in **b**, respectively. Number of rats in each group≥7. *$p<0.01$ *vs.* CON group, [†]$p<0.05$ *vs.* DM group, one way ANOVA
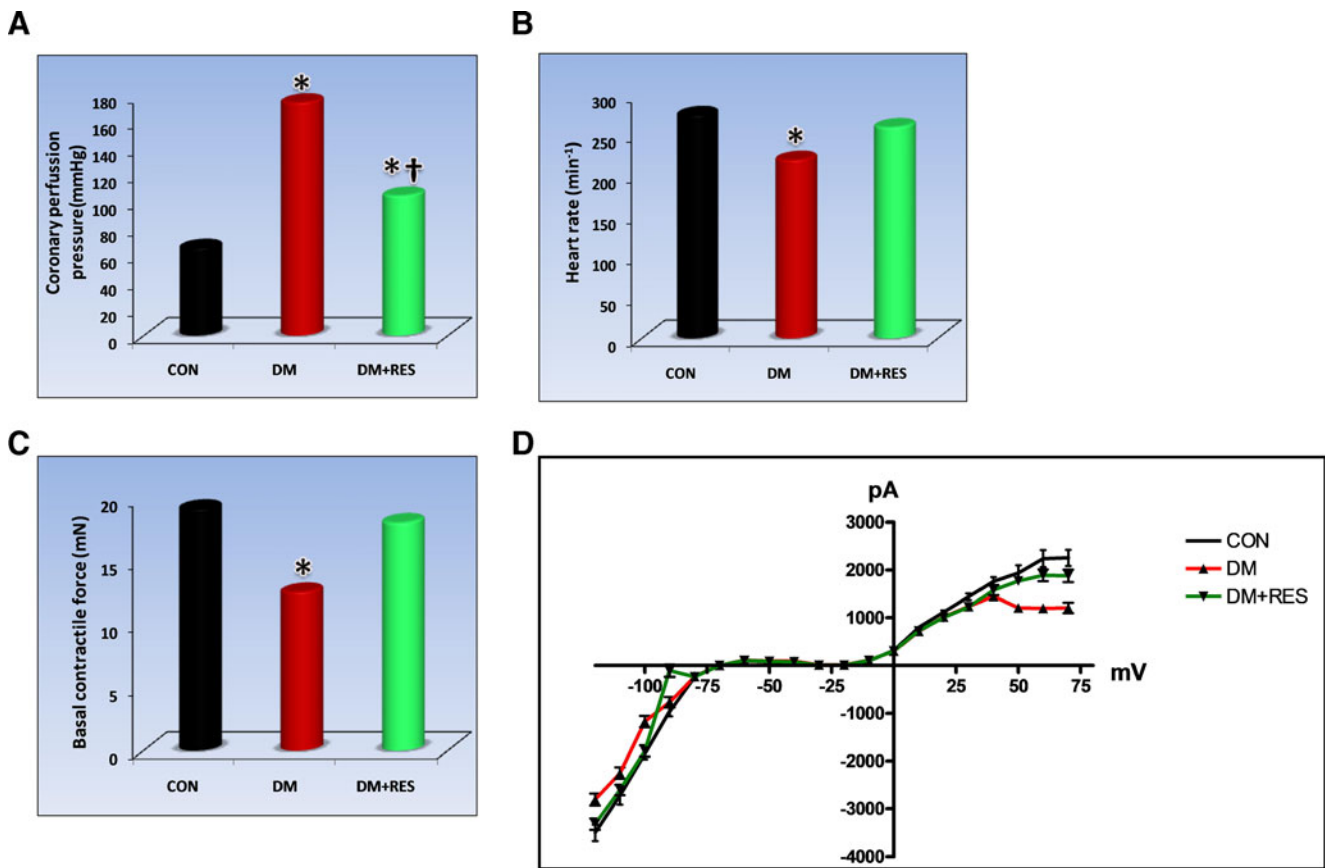
Fig. 5 Effects of resveratrol treatment on mechanical activity of the heart and K^+ currents of cardiomyocytes isolated from ventricle of the diabetic rats. (A) The effects of resveratrol treatment (2 mg/kg body weight, daily and orally for 4 weeks) on increased coronary perfusion pressure **a** and heart rate **b** as well as their basal contractile force **c** measured by using Langendorff-perfusion (during 60 min) system in STZ-induced diabetic rat hearts are given as means (±SEM) (for methods see (Turan et al. 1999)). Number of rats used in each group≥7. *$p<0.01$ vs. CON group, and †$p<0.05$ vs. DM group, one way ANOVA. **d** The effect of resveratrol treatment on diabetes-induced depressed K^+ currents (transient outward current, I_{to} and inward rectifier current, I_{K1}) were recorded by using whole-cell patch clamp recordings. From a holding potential of -80 mV, voltage pulses (duration of 600 ms) between -120 and $+70$ mV (with 10 mV steps) were applied at a frequency of 0.14 Hz. The mean cell capacitance varied between 140 and 150 pF for the groups without any significant difference between them. Current–voltage (I–V) relationships of the peak current densities (I_{to} and I_{K1}) in cardiomyocytes isolated from control (CON; $n=18$ cells from 5 rats), diabetic (DM; $n=20$ cells from 5 rats) and resveratrol-treated diabetic groups (DM+RES; $n=16$ cells from 4 rats). The current amplitudes were estimated for I_{K1} at -120 mV, and for I_{to}, which was estimated as the difference between peak and steady state currents elicited at $+70$ mV. Data points on the graphs represent mean (±SEM) values. *$p<0.01$ vs. Con group, and †$p<0.05$ vs. DM group, one way ANOVA

resveratrol alleviated diabetes-induced vasculopathy through attenuation of advanced glycation end product-receptor for advanced glycation end product-NF-kappaB signalling pathway (Jing et al. 2010).

In healthy humans, resveratrol supplementation at relatively low doses, significantly increased nuclear factor (erythroid-derived 2)-like 2 Nrf-2- binding activity, messenger RNA (mRNA) expression of the NAD(P)H dehydrogenase [quinone] 1 (NQO-1) and glutathione S-transferase pi 1 (GST-p1) genes, suggesting a strong anti-oxidant effect (Ghanim et al. 2011). The authors suggested that resveratrol reduces the oxidative and inflammatory responses of the high-fat high-carbohydrate meal and has potential to reduce the risk of atherosclerosis and diabetes through these mechanisms. Moreover, grape seed extract given over a 4-week period significantly improved markers of inflammation and glycemia and increased GSH a marker of oxidative stress in obese type 2 diabetic subjects at high risk of cardiovascular events (Kar et al. 2009). In similar patients, specifically trans-resveratrol, given at 5 mg daily for 4 weeks, significantly improved insulin sensitivity, lowered blood the glucose levels and delayed glucose peak following a standard meal. A decreased oxidative stress and increased AKT phosphorylation may have contributed to these effects (Brasnyo et al. 2011).

Recent basic animal studies We designed a study to seek and to compare the heart and aorta functions of normal
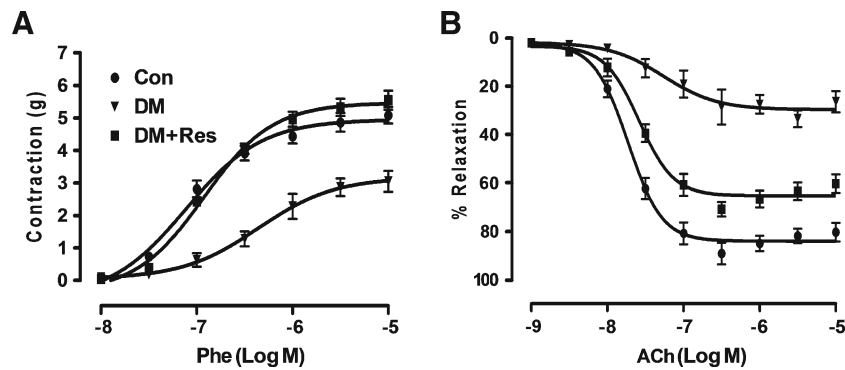
Fig. 6 Resveratrol treatment restored contractile response to phenyl-ephrine stimulation and acetylcholine-induced vasorelaxation of the endothelium-intact aortic preparations in diabetic rats. **a** Maximal percentage contractile responses of endothelium-intact aortic prepara-tions from STZ-induced diabetic rats to phenylephrine (Phe)-stimula-tions with respect to their basal tension. **b** Percentage relaxation responses to acetylcholine (ACh)-stimulations with respect to their

Phe (10^{-5} M)-precontraction in the similar aortic preparations. The methods used in this group of experiments were previously described (Zeydanli et al. 2011). Number of experiment is 7–9 per group. The abbreviations are the following: CON; control group, DM; untreated diabetic group, DM+RES; resveratrol treated diabetic group. $^{*}p<0.01$ vs. Con group, and $^{†}p<0.05$ vs. DM group, one way ANOVA

versus STZ-induced diabetic male rats after resveratrol treat-ment (2.5 mg/kg/day for 4 weeks) using electrophysiologic data as well as biochemical analysis. Resveratrol-treated diabetic rats demonstrated significant reduction in glucose level and increase in plasma insulin level as compared to the non-treated diabetic animals (Table 1). Increases in thrombin-induced aggregation and thromboxane B2 of the platelets from the diabetic rats were prevented with resver-atrol treatment (Fig. 4A and B). The systemic antioxidant like effect of resveratrol treatment of diabetic rats such as serum MDA and GSH/GSSH levels are also given in Table 1. Resveratrol treatment of diabetic rats improved global heart function including coronary perfusion pressure and heart rate (Fig. 5A to C) as well as it induced a normali-zation in depressed K^{+} currents (transient outward current, I_{to} and inward rectifier current, I_{K1}) recorded from freshly isolated cardiomyocytes (Fig. 5D). In the same group of diabetic rats, it is shown that both direct and alpha-adrenergic receptor-mediated aortic contractile responses as well as endothelium-dependent vasodilatory responses were preserved with resver-atrol treatment (Fig. 6A and B). It has been recently shown that endothelium removal abolished the significant difference

between resveratrol-treated and untreated diabetic groups re-garding contractile response to phenylephrine while endothelium-dependent relaxation to acetylcholine was signif-icantly higher in resveratrol-treated diabetic rats as compared to the diabetic group (Roghani & Baluchnejadmojarad 2010). In addition, the oxidant stress/nitrosative stress levels in both heart and aorta were found to be normalized in the resveratrol-treated group compared to the untreated one (Tables 2 and 3). These results indicate that resveratrol prevents cardiac and vascular dysfunction in diabetes due to its effect in oxidant stress/anti-oxidant defense balance and their related signalling pathways. In healthy rats, the resveratrol-induced improvement of endo-thelial reactivity and inhibition of superoxide production were gender independent (Soylemez et al. 2009). This is to compare with its similar protective effects in male and female stroke-prone spontaneously hypertensive rats (Mizutani et al. 2001).

Concluding remarks

Most of the research on resveratrol has been performed on animals or in laboratory studies involving tissue extracts,

Table 2 Soluble sulphydryl, nitrite and thioredoxin reductase levels measured in the heart tissues

	Soluble sulphydryl (µmol/g tissue)	Nitrite (nmol/mg protein)	Thioredoxin reductase (mU/mg tissue)
CON ($n=7$)	5.4±0.2	16.2±0.3	80.2±1.3
DM ($n=7$)	3.1±0.2*	30.0±0.5*	61.3±3.0*
DM+RES ($n=7$)	4.8±0.3†	25.9±0.7*,†	76.2±2.2*,†

The groups have similar abbreviations and properties as defined in Table 1; n, number of hearts. Values are expressed as mean ± SEM. $^{*}P<0.05$ vs. CON group, and $^{†}P<0.05$ vs. DM group, by ANOVA

Table 3 Endothelin-1 (ET-1), protein kinase C (PKC), cAMP and nitrite levels in aortic tissues

	ET-1 (fmol/mg tissue)	Total PKC (nmol/mg protein)	cAMP (pmol/mg tissue)	Nitrite (nmol/mg tissue)
CON ($n=7$)	45.1±1.2	16.2±0.3	3.3±0.1	600±14
DM ($n=7$)	23.6±2.0*	18.0±0.5	4.9±0.2*	490±18*
DM+RES ($n=7$)	34.8±1.3*,†	15.9±0.7	3.9±0.2*,†	532±20*,†

The groups have similar abbreviations and properties as defined in Table 1; n, number of aortas. Values are expressed as mean ± SEM. $^{*}P<0.05$ vs. CON group, and $^{†}P<0.05$ vs. DM group, by ANOVA

and, for this reason, scientists are not yet certain about the health benefits of resveratrol for humans who consume ordinary amounts of resveratrol-containing foods. Moreover, it should be considered that although experimental animal studies and other in vitro experimental results are critical steps for testing safety and efficacy during preclinical drug design with resveratrol, they cannot have perfect denouncement for its ultimate success in human medicine. Clearly, animal data are not sufficient to determine the safety and efficacy of resveratrol in humans; it is needed short-term safety trials. Due to the literature documents, there is enough experimental data for the future clinical development of resveratrol that doses of up to 5 g/day/month are safe and reasonably well-tolerated (Baur & Sinclair 2006; Vang et al. 2011; Boocock et al. 2007; Kennedy et al. 2010; Lekakis et al. 2005; Marques et al. 2009; Nguyen et al. 2009; Smoliga et al. 2011a; Smoliga et al. 2011b; Wallenborg et al. 2009). However, it is becoming increasingly clear that resveratrol has two faces. On one hand, it protects cells by potentiating a survival signal; on the other hand, it selectively kills cancer cells. Resveratrol behaves as an antioxidant, yet it can induce redox signaling. Moreover, the same compound triggers a survival signal in the ischemic tissue by inducing antiapoptotic genes and blocks apoptosis in ischemic heart as well as protect heart and vessels against diabetes-induced organ damage (Dudley et al. 2009).

Besides these hormometic effects it should be also considered before translating in vitro or tissues studies to human that polyphenols can also oxidize readily in cell culture media, and several claims of the cytotoxic effects of flavonoids on malignant, and other, cells in culture may have been led astray by this artefact. Oxidation generates H_2O_2, quinones and semiquinones that can contribute to, and sometimes entirely account for cytotoxicity (Halliwell 2007). Moreover, redox balance displayed daily variations related to physiological lipid peroxidation rhythm in mice and even in mammals. Of note resveratrol exhibits pro-oxidative properties leading to an increase in intracellular superoxide. When administred to rats during the activity phase (at dark), resveratrol behaved as a powerful anti-oxidant in the heart, liver and kidney, while it exerted pro-oxidant effects when administred during the rest phase (at light). These opposite effects of resveratrol occur at a concentration (3 μM) devoid of any harmful or toxic effects (Gadacha et al. 2009).

An expanding body of preclinical evidence suggests resveratrol has the potential to impact a variety of human diseases. Published clinical trials have largely focused on characterizing the pharmacokinetics and metabolism of resveratrol. As mentioned in two recent review articles by Patel et al. (Patel et al. 2011) and Smoliga et al. (Smoliga et al. 2011b) although a numerous amount of experimental

studies including their promising results with resveratrol and since there is presently very little evidence of pharmacological activity in humans, the number of clinical trials and their highlighten results are yet very limited. Due to a search of a database (http://clinicaltrials.gov/; 120) as they mentioned, there are 16 studies involving resveratrol that are either active or recruiting besides 6 more that have recently been completed. In these trials, the basic idea was to investigate the potential role of resveratrol in the management of type 2 diabetes, obesity, aging, and cancer. Unfortunately, it is not included any particular clinical trial with resveratrol role in cardiovascular diseases. An important clinical study including a double-blind and placebo-controlled crossover was undertaken recently by Kennedy et al. (Kennedy et al. 2010) which demonstrated the effects of resveratrol, using single oral doses (either 250 of 500 mg) on cerebral blood flow variables and cognitive performance in humans. Resveratrol induced a higher blood flow in the prefrontal cortex as indexed by total hemoglobin concentration. This study is the first promising indication associated with benefits of resveratrol in the circulatory system in humans, and is confirmed by the recent demonstration of resveratrol-increased NO responsiveness in the human brachial artery (Wong et al. 2011).

The *in vitro* dose dependency data besides *in vivo* results as well as clinical findings are further discussed in recent review articles (Petrovski et al. 2011; Vang et al. 2011; Gorbunov et al. 2011; Bertelli & Das 2009). These results provide a common mechanism for and support the beneficial effect of resveratrol under pathological conditions induced by oxidative stress in biological tissues including humans. However, the published evidence is not strong enough to justify a recommendation for the administration of resveratrol to humans, beyond the dose which can be achieved from dietary sources (Vang et al. 2011). Animal data are promising in prevention of various cancer types, coronary heart diseases and diabetes, which strongly indicate the need for more human clinical trials, particularly devoted to cardiovascular diseases.

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