Minireview

Potential of resveratrol in the treatment of heart failure

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Abstract

The concept of food has expanded beyond its traditional role of survival and hunger satisfaction, to include a role in the prevention and treatment of disease. Polyphenols are classes of compounds that are synthesized by plants to serve a wide variety of functions including growth, pollination and defense. These compounds have recently received increased attention in medical research. In this group, one of the most studied has been resveratrol (3,5,4'-trihydroxystilbene), a polyphenol, which is found predominantly in grapes and berries. Over the past two decades, researchers have studied the ability of resveratrol to prevent or reverse the development of abnormalities in heart structure and function in animal models of heart disease and heart failure. The results from animal studies have been promising, and very recently, this knowledge has been translated into examining the efficacy of resveratrol in humans with heart disease/failure. In this review we will discuss the current status of resveratrol research on cardioprotection.

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Introduction

Heart failure therapy

Heart failure continues to be a significant cause of cardiovascular mortality. It has aligned itself with chronic disease management strategies, and remains the most common cause of hospitalizations and readmissions in North America and Europe (Jhund et al., 2009; Bueno et al., 2010; Yeung et al., 2012; Heidenreich et al., 2012). Affected individuals can also be plagued with a poor quality of life even when receiving appropriate medical and device optimization (Murdoch et al., 1998; Senni et al., 1999; Hobbs et al., 2002).

Heart failure is a complex multifactorial syndrome resulting from the heart's inability to pump adequate circulation to meet the metabolic demands of organs and tissues. Some potential contributors to the development of heart failure include hypertension, ischemic heart disease, diabetes, valvular heart disease and idiopathic cardiomyopathy. Regardless of the clinical scenario, the pathophysiologic compensatory response results in the remodeling of the heart. The initial hypertrophic response is beneficial; however, sustained hypertrophy leads to heart failure. On a microscopic level this entails increases in myofibrillar and mitochondria, followed by disruptions in cellular organization featuring a predominance of myofibrils and loss of contractile elements. Following the compensatory phase, the persistent pressure or volume overload overwhelms the Frank Starling mechanism resulting in the “exhaustion phase” leading to myocyte necrosis via lysis of myofibrils, distortion of the sarcoplasmic reticulum and fibrosis (Meerson, 1969; Ferrans, 1983). Mechanisms of this pathophysiologic response are potential therapeutic targets and include oxidative stress, fibrosis, apoptosis and necrosis. These intricate pathways and neurohumoral responses are responsible for the transition from the compensated stage of hypertrophy to the decompensated stage of heart failure (Carabello, 2002; Frey and Olson, 2003; Selvetella et al., 2004; Frey et al., 2004; Opie et al., 2006).

Clinical practice guidelines over the past decade highlight drugs targeting the sympathetic nervous system (β-adrenergic receptor blockers) and the renin–angiotensin aldosterone system (angiotensin converting enzyme inhibitors and alternatively the angiotensin II receptor blockers) as the cornerstone of medical therapy for systolic heart failure (Lindenfeld et al., 2010; McMurray et al., 2012; Mckelvie et al., 2013; Yancy et al., 2013). Angiotensin converting enzyme inhibitors decrease outcomes of hospitalization, mortality and combination endpoints in systolic heart failure from 15 to 27% in comparison to placebo (The CONSENSUS Trial Study Group, 1987; The SOLVD Investigators, 1991; The SOLVD Investigators, 1992; Flather et al., 2000). β-Adrenergic receptor blockers decrease mortality by approximately 34% over placebo, and decrease hospitalizations by 28–36% (The Cardiac Insufficiency Bisoprolol Study II, 1999; MERIT-HF, 1999; Hjalmarson et al., 2000; Packer et al., 2001, 2002). Mineralocorticoid receptor antagonists have also become a fundamental component of the standard care for many inpatient and ambulatory heart failure patients. They are indicated in mild to severely symptomatic systolic heart failure patients, decrease mortality by 30–37% and also significantly reduce hospitalizations (Pitt et al., 1999; Zannad et al., 2011). Newer agents such as ivabradine and myosin agonists will likely also impact patient care and outcomes (Swedberg et al., 2010; Malik et al., 2011). Adjunctive to medical therapy, device optimization of systolic heart failure patients includes screening for candidacy for primary prevention implantable defibrillators and cardiac resynchronization which have additive morbidity and mortality benefits (Moss et al., 2002, 2009; Bardy et al., 2005; Tang et al., 2010; Bristow et al., 2004; Cleland et al., 2005).

Despite the above regimen of optimal medical and device management, remodeling often continues, symptoms progress and death can occur. To date, the strategies proven in systolic heart failure patients have all failed to demonstrate a significant mortality benefit in the setting of heart failure with preserved ejection fraction (diastolic dysfunction). These include CHARM-Preserved, PEP-CHF, I-PRESERVE and the recently presented TOPCAT trial (Yusuf et al., 2003; Cleland et al., 2006; Massie et al., 2008; Desai AS et al., 2013). As a growing proportion of heart failure cases consists of these clinically distinct and heterogeneous groups of patients with preserved ejection fraction, the challenge becomes evaluating novel treatment options (Roger, 2013). Accordingly, it is essential to explore newer strategies to inhibit the development or to reverse cardiac hypertrophy and heart failure after it has developed. In this context, nutraceuticals appear to have a great potential.

Nutraceuticals

The modern concept of food has expanded beyond its traditional role in basic nutrition and satiety, to include the prevention and treatment of disease (Alissa and Ferns, 2012). By definition, nutraceuticals are dietary supplements that provide a concentrated form of the bioactive agent (in whole foods) used to improve health in dosages which are generally unattainable through normal diet. Evidence from epidemiological, in vivo, and clinical studies indicates that nutraceuticals can reduce the risk of cardiovascular diseases (Alissa and Ferns, 2012). Dietary fibers, polyunsaturated fatty acids, phytosterols, vitamins and polyphenols are some of the groups of compounds that have been reported to have cardiovascular benefits.

Polyphenols

Polyphenols are a family of compounds synthesized by plants, that have received increased attention in medical research (Habauzit and Morand, 2012; Quinones et al., 2013). These compounds serve a wide variety of functions in plants ranging from growth to pollination to defense. Depending on the number of phenol rings, and the structural properties of their binding to each other, polyphenols are divided into subclasses including phenolic acids, flavonoids, stilbenes and lignans. Among the polyphenols, one of the most studied has been resveratrol, and, it belongs to the subclass, stilbenes. Resveratrol is a phytoalexin produced by plants, especially during fungal infections, UV radiations and other environmental stresses such as cold temperatures (Juhasz et al., 2010). Resveratrol is present in significant amounts in a few edible plants such as grapes, peanuts, soy beans, pomegranates, mulberry and bilberry (Giovannozzo et al., 2012), and to a lesser extent in non-edible plants such as pine, eucalyptus and spruce trees, and in a few flowering plants, such as Veratrum grandiflorum and Veratrum formsomaunum (Pervaiz, 2003; de Lorgeril et al., 2003). Resveratrol exists in two structural isomeric forms, cis- and trans-resveratrol (Fig. 1) (molecular weight: 228.24); both isomers are lipophilic in nature (Wallrath et al., 2002).

Fig. 1. A—Structure of cis-resveratrol. B—Structure of trans-resveratrol.
Resveratrol as a cardioprotective agent in animal studies and clinical trials

Moderate red wine consumption has been shown to be associated with the reduced incidence of cardiovascular disease among the French population, and the theory suggested by this epidemiological study is popularly known as the ‘French paradox’ (Renaud and de Lorgeril, 1992). The association of resveratrol to French paradox generated a greater interest in resveratrol research wherein the efficacy of purified resveratrol or food containing significant amount of resveratrol was extensively investigated in a wide range of cell or animal models of heart diseases (Juhasz et al., 2010). Given the limited scope of this review, only in vivo animal studies and recently reported human clinical trials will be discussed in this review.

Animal studies

Hypertension

Resveratrol has been well studied in the context of preventing/reversing cardiovascular defects caused by elevated blood pressure in various experimental models of hypertension. Some of these studies have demonstrated a significant reduction in blood pressure along with improvement in cardiac structure or function (Liu et al., 2005; Miattle et al., 2005; Dolinsky et al., 2013a). For instance, administration of resveratrol significantly attenuated the increased systolic blood pressure and arrested the development of cardiac hypertrophy in partially nephrectomized rats (Liu et al., 2005). Similarly, in another study carried out on fructose-fed rats, resveratrol supplementation prevented the increase in systolic blood pressure and cardiac hypertrophy (Miattle et al., 2005). Recently, Dolinsky and colleagues demonstrated that a high dose resveratrol was able to attenuate high BP and subsequent cardiac remodeling in two different hypertensive animal models: spontaneously hypertensive rats (SHRs) and the angiotensin (Ang)-II infused mouse (Dolinsky et al., 2013a). From these three studies reporting anti-hypertensive effects of resveratrol, it may be concluded that resveratrol is capable of preventing or arresting the development of hypertension, if it is administered prior to the development of hypertension.

Considering the fact that myocardial hypertrophy is one of the hallmarks of sustained hypertension, many studies have investigated the potential of resveratrol in preventing/arresting hypertrophy and associated cardiac dysfunction irrespective of the changes in blood pressure in different hypertensive animal models (Dolinsky et al., 2009; Wojciechowski et al., 2010; Thandapilly et al., 2010). While the Wojciechowski study demonstrated the ability of resveratrol in arresting cardiac hypertrophy and associated dysfunction in rats subjected to abdominal aortic banding procedure, the other studies reported the cardioprotective efficacy of resveratrol in young SHRs. The results from the above studies showing the effectiveness of resveratrol in preventing cardiac dysfunction even without reducing hemodynamic load suggest that resveratrol may act directly on the myocardial tissue to render cardioprotection.

A few other studies have also investigated whether resveratrol is able to reverse cardiac hypertrophy and contractile dysfunction once it is developed (Juric et al., 2007; Chan et al., 2011; Toklu et al., 2010; Rimbaud et al., 2011; Thandapilly et al., 2013). In the first study, the regression of myocardial hypertrophy and diastolic impairment was achieved in the aortic banded rat by resveratrol treatment (Juric et al., 2007), whereas Chan et al. observed a significant improvement in cardiovascular function in young SHR upon resveratrol administration (Chan et al., 2011). Similarly, resveratrol proved to be effective in improving cardiovascular function in two-kidney, one-clip hypertensive rats (Toklu et al., 2010). Resveratrol was also potent in reversing cardiac hypertrophy and contractile dysfunction in a more pronounced model of heart failure induced by hypertension where it reversed cardiac hypertrophy and associated contractile dysfunction (Rimbaud et al., 2011). A recently conducted study from our laboratory also demonstrated resveratrol’s efficacy in reversing cardiovascular abnormalities in 28 weeks old SHR when it is administered in conjunction with a blood pressure lowering agent (Thandapilly et al., 2013). These studies indicate a significant effect of resveratrol in reversing the cardiovascular structural functional abnormalities associated with hypertension, which is believed to be achieved only by frontline pharmacological agents.

The potential of resveratrol in preventing as well as reversing cardiovascular defects caused by elevated blood pressure has been adequately examined. It is interesting to note that the studies have been conducted on several different animal models of hypertension, including essential hypertension (SHR), secondary hypertension (nephrectomized rats), diet induced hypertension (DOCA-salt sensitive rats) and surgically induced hypertension (abdominal aortic banded rats). The studies mentioned above have used a wide range of doses and reported cardioprotection with or without lowering of elevated blood pressure. Overall, these studies show that resveratrol has the potential to prevent/reverse myocardial defects independent of the change in hemodynamic load, and render cardioprotection by directly acting on the myocardium. However, it has to be taken into account that in all of the aforementioned studies, resveratrol treatment was of short term duration.

Ischemic heart disease

Resveratrol has been reported to protect the myocardium from acute and chronic ischemia through various mechanisms, including the inhibition of platelet aggregation and thereby preventing myocardial infarction (MI), prevention of ischemic reperfusion injury of the myocardial tissue via preconditioning, and triggering the regeneration of infarcted heart tissue. To date, three studies have investigated the efficacy of resveratrol as a preconditioning agent in various animal models of ischemic heart disease (Chen et al., 2008; Hung et al., 2004; Robich et al., 2010). In one of the studies, resveratrol was able to prevent cardiac arrhythmia and infarct size in rats with left coronary artery ligation induced ischemia reperfusion injury when administered prior to the surgery (Hung et al., 2004). Likewise, Chen et al. (2008) found that resveratrol administration prior and post-coronary artery ligation surgery significantly prevented the progression of cardiac hypertrophy induced by myocardial infarction and reduced the infarct size. Similar findings were also reported in a separate study conducted in Yorkshire swine, where resveratrol pre-treatment improved myocardial perfusion in a swine model of chronic myocardial ischemia (Robich et al., 2010).

Although resveratrol has been widely proposed as a preconditioning agent to prevent the ischemic heart events, it is of great clinical significance to assess its potency as a therapeutic agent to reverse the cardiovascular complications associated with ischemic heart disease. Few studies have specifically examined the potential of resveratrol in reversing the post-ischemic cardiac impairment (Lin et al., 2008; Xuan et al., 2012; Kanamori et al., 2013). In a surgical model of MI, researchers observed a significant reduction in infarct size and an improvement in the left ventricular systolic and diastolic functional parameters with resveratrol treatment (Lin et al., 2008). Similarly, Xuan et al. (2012) study also reported that resveratrol was effective in reducing the deleterious effects of fractalkine on myocardial ischemia and thereby preventing subsequent cardiac remodeling in mice with left-sided thoracotomy and left coronary artery ligation. To specifically evaluate the efficacy of resveratrol on infarcted failing heart, a group of investigators from Japan studied the cardioprotective effects of resveratrol on mice subjected to left coronary artery ligation. The animals with established heart failure were supplemented with resveratrol for four weeks post-infarction. The results showed that resveratrol was capable of reversing remodeling in hearts with large, old myocardial infarction (Kanamori et al., 2013).

The potential of resveratrol in preventing as well as reversing defects in cardiac structure and function has been examined in both acute and
chronic settings of myocardial ischemia or myocardial ischemia reperfusion. Resveratrol mediated cardioprotection was generally observed in several species ranging from mice to pig, and from very low to high doses, with the exception of the study reported by Burstein et al. (2007). It is impressive to note that the very low dose (1 mg/kg/day) of resveratrol used in certain studies (Kaga et al., 2005; Lin et al., 2008) is much lower than the dietary dose. It must be noted that in all of the aforementioned studies, resveratrol treatment was of short term duration. Considering the fact that ischemic heart damage due to coronary heart disease accounts for the majority of the cardiovascular deaths, more well organized animal studies assessing cardiac structural and functional remodeling are needed to substantiate the beneficial effects of resveratrol against ischemic heart disease.

Cardiomyopathy

The cardioprotective role of resveratrol has also been evaluated in different animal models of cardiomyopathy. Since resveratrol has been shown to possess immunomodulatory activities, one group of investigators examined whether resveratro may favorably modulate the myocardial injury induced by myocarditis (Yoshida et al., 2007). This study showed a significant reduction in left ventricular hypertrophy and improved systolic function in rats with myocarditis induced by cardiac myosin immunization. Another group also observed improvement in cardiac performance with resveratrol supplementation in a mouse model of chronic viral myocarditis (Wang et al., 2009).

Resveratrol has also been investigated for its ability to limit the deleterious effects on heart tissue caused by some of the very effective cancer drugs which have been restricted from the clinics due to their dose-dependent toxicity (Zhao et al., 2008; Tatlidede et al., 2009). For instance, Zhao and co-workers showed that resveratrol was able to improve the abnormalities in electrical activity and cardiac structure in a mouse model of arsenic trioxide-induced cardiomyopathy. Similar findings were also reported in two different studies using doxorubicin-induced cardiomyopathy model, where an improvement in cardiac function with resveratrol treatment was observed (Wang et al., 2009; Pinarli et al., 2013).

Unlike the current heart failure therapies which only target neurohumoral factors and not the reactive oxygen species, the distinct antioxidant protective function of resveratrol was explored by Tanno and co-workers in mice deficient in mitochondrial manganese superoxide dismutase (Tanno et al., 2010). In this study, a relatively high dose of resveratrol preserved cardiac function, and significantly improved survival in mice with dilated cardiomyopathy and chronic heart failure. The efficacy of resveratrol on cardiac complications due to cancer has also been investigated recently in rat model of cardiomyopathy induced by C26 adenocarcinoma tumors (Shadfar et al., 2011); where resveratrol prevented cardiac atrophy. Another study investigated whether resveratrol has any cardioprotective effects on endotoxin-induced myocardial injury using a mouse model; the results demonstrated that resveratrol treatment significantly attenuated LPS-induced myocardial injury in mice (Hao et al., 2013).

A few studies have examined cardioprotection in animal models of virus or toxin induced cardiomyopathy. In general, resveratrol administration has improved cardiac outcomes in all the above studies. A wide range of resveratrol doses have been used in these studies, and treatment has been for both short and long duration. It is important to note that resveratrol treatment was effective in a long-term study conducted by Tanno et al. in a model of overt heart failure (Tanno et al., 2010). Put together, these findings suggest a strong potential for resveratrol in treating cardiomyopathies.

Obesity and diabetes

Cardiovascular disease is a very important comorbidity among the obese and diabetes population. Resveratrol being an antioxidant and metabolic regulator combined with the cardioprotective properties would be an ideal molecule to be used in the treatment of obesity and diabetes. Resveratrol improved systolic heart function in streptozotocin (STZ) induced diabetes in mice (Sulaiman et al., 2010) and rats (Huang et al., 2010). In another study with leptin deficient animal model of diabetes, resveratrol treatment improved both systolic and diastolic heart functions (Zhang et al., 2010). In a more recent study with diet induced obesity in rats, resveratrol administration reversed diastolic dysfunction (Louis et al., 2012), while another study done in a similar animal model showed that resveratrol treatment in obese mice decreased cardiac hypertrophy and improved diastolic function (Qin et al., 2012). In both Louis et al. and Qin et al. studies, animals were reported to have characteristics of early stage type II diabetes.

To date, there is limited data validating the effectiveness of resveratrol against cardiovascular complications associated with obesity and diabetes, both types I and II. However, the few studies completed have showed in general an improvement in metabolic parameters as well as in cardiac structure and function in animal models of obesity and type I and type 2 diabetes. Furthermore, these studies used low and high doses of resveratrol treatment which ranged from short to relatively long-term resveratrol administration.

Human clinical trials

Building on the concept of combinational treatment approaches, new alternative or adjuvant therapeutic strategies using the potential nutra-ceutical candidate resveratrol have been explored for primary or secondary prevention of heart diseases (Tome-Carneiro et al., 2013a). As discussed in the above sections, the preclinical studies reported beneficial effects of resveratrol in improving CVD, however, only the clinical evaluation of resveratrol as a new cardioprotective therapeutic agent in CVD patients will enable us to determine its true potential. Compared to the vast number of preclinical studies which have reported the beneficial effect potential of resveratrol in cardiovascular disease prevention and reversal, the number of human clinical studies which have investigated the effects of resveratrol in individuals affected with CVD is few (Tome-Carneiro et al., 2013a; Smoliga et al., 2011). Among the cardiovascular human clinical trials, only one has examined the effects or resveratrol supplementation on heart structure and function in patients with heart disease (Magyar et al., 2012), while the other trials studied cardiovascular risk factors, but not heart structure or function in a clinical scenario (Tome-Carneiro et al., 2013a). Given the limited scope of the review, only the human cardiovascular clinical trials will be briefly discussed.

A 3 month randomized, double-blind, placebo controlled human trial with 40 post-infarction Caucasian patients (26 men and 14 women) investigated the role of resveratrol in secondary prevention of CVD (Magyar et al., 2012). The results showed that addition of a low dose of resveratrol to standard medication resulted in added protection as evident by a significant improvement in diastolic heart function, and a marginal recovery of systolic heart function (when compared to the placebo group). Additional effects observed with resveratrol treatment included improved endothelial function, increased red blood cell deformability, decreased platelet aggregation and decreased LDL cholesterol levels.

In a series of clinical trial reports, Tome-Carneiro et al. described the beneficial effects of intervention with low dose resveratrol containing grape extract in reducing the level of inflammatory, fibrinolytic, and atherogenic biomarkers in patients undergoing treatment for primary prevention of CVD as well as patients with stable coronary artery disease (Tome-Carneiro et al., 2012a,b, 2013b,c). Resveratrol significantly decreased the pro-inflammatory and fibrinolytic markers in patients being treated for primary prevention of CVD in this study. As these patients were under the treatment with statins which are one of the effective therapeutic strategies to lower atherogenic risk factor markers, it appears that resveratrol complements the standard medications for...
CVD. In a similar study in patients with stable coronary artery disease, the same group reported significant improvement in the level of the anti-inflammatory molecule adiponectin along with a decrease in plasminogen activator inhibitor-1 level in resveratrol treated group (Tome-Carneiro et al., 2013b). In a followup study involving a subpopulation of the same cohort from the above reported trials, downregulation of pro-inflammatory gene expression was observed (Tome-Carneiro et al., 2013c). Apart from that, transcription factors and miRNAs linked to inflammatory responses have also been affected by the resveratrol treatment in the subpopulation of male CAD patients with type 2 diabetes mellitus and hypertension, which further substantiated the overall anti-inflammatory property of resveratrol (Tome-Carneiro et al., 2013c). Recently, a randomized, double-blinded, active-controlled, parallel clinical trial using resveratrol and calcium fructoborate was conducted in patients with angina pectoris. Data from this novel combination therapy trial suggested that resveratrol treatment resulted in a decrease in inflammatory markers and improvement in lipid profile. Also, synergistic action of resveratrol and calcium fructoborate was observed from the results of this clinical trial (Militaru et al., 2013).

The outcomes examined in the aforementioned clinical trials have been successful with the use of low dose resveratrol. However, only one trial has assessed heart structure and function. Therefore, evidence supporting the cardioprotective property of resveratrol in CVD patients is indeed limited and not elaborate. As well, long term effects of resveratrol on cardiac structure and function in patients with cardiovascular disease are not known, the lone human study conducted by Magyar et al. (2012) was of a short duration. According to clinical trial registries, there are human cardiovascular disease/heart failure trials listed which are testing or propose to examine the efficacy of resveratrol (ISRCTN02337806, NCT01185067, NCT01914081) on heart structure and function in addition to other cardiovascular risk factors. The results of these ongoing/future clinical trials will give us more insight into the potential future of resveratrol as an adjunct in heart failure therapy.

Conclusions from animal and human studies

There is a large amount of research data published with food derived molecules including resveratrol which has demonstrated strong cardioprotective benefits. In this context, the beneficial effects of resveratrol have been reported with a wide range of doses and treatment time including length of treatment pre- or post-disease. It is surprising to note that in the studies discussed in this review, resveratrol has been shown to confer benefits at very low doses (10 μM/kg/day) and all the way up to 4 g/kg/day. Unfortunately, this has contributed to increased uncertainty in the mind of a researcher regarding the dose and time period to choose for the particular animal model. Nevertheless, majority of the studies were conducted using a low to moderately high dose (1–100 mg/kg/day) of resveratrol. Doses up to 1–2 mg/kg/day in rats and up to 10 mg/day in humans could be considered a dietary dose, and the desired effects may be obtained with consumption of certain resveratrol rich foods or drinks. A non-dietary dose is referred to as a therapeutic dose, which could only be delivered with administration of resveratrol supplements. Dietary doses of resveratrol have been promising, however, most of the animal studies that used a therapeutic dose of resveratrol have reported robust effects when compared to studies using dietary doses. However, in humans, low dose resveratrol was found to be effective.

The important points to note are that the effectiveness of the dose depends largely upon the mode of delivery, animal model used in the study, and the parameters that are being studied. The bioavailability of resveratrol and its uptake by the heart solely depends on its concentration in the circulation. Resveratrol has a very low bioavailability that does not increase incrementally with the dose administered. Resveratrol bioavailability is limited at the site of absorption in the gut. Therefore the route of resveratrol administration will certainly influence the concentration of resveratrol available in the circulation. For example a moderately high dose (100 mg) of resveratrol administered orally will result in almost the same blood concentration as the very low dose (10 μM) of resveratrol administered intravenously into the circulation.

The length of resveratrol treatment has also been reported to span a wide range starting from 15 min to 1 year. It is difficult to see a robust effect within a short period of treatment, however, if one were to look into molecular changes or antioxidant and anti-inflammation status, then a shorter treatment (few days) may be enough. When observing changes in cardiac structure and function with resveratrol, it is preferable to have a longer treatment period to ensure that a statistically significant difference is achieved at the end of the study. Resveratrol has not been reported to have toxic effects at moderately high doses (200–500 mg/kg/day) in animals, and it may therefore be safe to administer resveratrol for a longer period.

Finally, the time for initiating the treatment is also critical. Resveratrol has been effective most of the time when treatment started well before the induction of disease in animal models. Pretreating the animals will help to create a strong antioxidant environment thereby minimizing the damage due to oxidative stress. However, in certain studies the aim was to evaluate the potential of resveratrol to manage or reverse the disease. Resveratrol has been effective in animal studies when the treatment started post-disease too, but not as much as prior to the induction of disease. However, resveratrol has shown much more promise in clinical trials when the treatment began post-disease. This capability will certainly increase the clinical relevance of resveratrol because in most cases clinicians begin to treat the patients well after the development of disease.

To conclude, there is no guarantee that a particular dose and length of treatment will be effective in a particular model of disease. The effectiveness of drugs varies from person to person and depends on many other factors such as age and overall health of the patient, intensity of disease and other socioeconomic factors. Accordingly, careful assessment must be done to conclude which dose and length of treatment are appropriate for a particular type of disease.

Resveratrol—evidence for lack of cardioprotection

Despite the wealth of evidence supporting the benefits of resveratrol on the heart in the settings of heart disease, there are two studies which have reported that it may be ineffective in certain pathological conditions. Wojciechowski et al. reported that resveratrol treatment did not prevent or reverse, respectively, cardiac hypertrophy in rats subjected to aortocaval shunt surgery, the aortocaval shunt rat being an animal model of valvular heart disease. A few years later, Louis et al. reported that resveratrol treatment was ineffective in reversing impaired diastolic heart function in obese resistant rats which are characterized by insulin resistance and hyperglycemia (Louis et al., 2012).

It must be noted, however, that the dose of resveratrol used in the aforementioned studies (Wojciechowski et al., 2010; Louis et al., 2012) was a low dose, accordingly, whether a higher dose would offer cardioprotection is not known.

Mechanism of action of cardioprotection with resveratrol

Resveratrol, like other polyphenols, is reported to act on several signaling pathways and molecular targets, and therefore the mechanism of its action is considered to be pleiotropic in nature (Kishimoto et al., 2013; Granados-Soto, 2003). In the current context, the cardioprotection observed in the earlier mentioned studies in the previous section is not the resultant of resveratrol mediated activation/inhibition of one or two pathways or a few molecular targets, but a sum of the effects on several signaling pathways/molecular targets. The mechanism of action of resveratrol’s exhibited cardioprotective properties involves antioxidant and anti-inflammatory effects and specific targets such as AMPK, SIRT 1 and nitric oxide (NO) (Wu et al., 2001). Nitric oxide is an endogenous cardioprotective molecule, and its concentration usually decreases in cardiovascular pathological conditions (Forstermann and Sessa, 2012).
Resveratrol treatment in animals with cardiovascular disease has been reported to recover NO levels (Liu et al., 2005). NO mediated vasodilation aids in reducing blood pressure which in turn reduces the load on the ailing heart and aids the recovery. Accordingly, NO might be a key molecule in resveratrol mediated cardioprotection. Activation of nitric oxide synthases (eNOS), especially endothelial NOS (eNOS), is a critical step towards the increase in NO and resveratrol has been reported to trigger eNOS activation (Miatello et al., 2005; Dolinsky et al., 2013a). Another important target of resveratrol, AMPK, is also a key player in the generation of NO. LKB1 is a molecule that is upstream to AMPK, which has been reported to be upregulated with resveratrol treatment (Dolinsky et al., 2013a; Dolinsky et al., 2009; Kanamori et al., 2013).

SIRT 1 is also claimed to be a target of resveratrol (Tanno et al. 2010) although the evidence for beneficial cardiovascular effects from in vivo studies is less convincing. Resveratrol mediated improvement in cardiac function was associated to SIRT 1 related increase in SERCA 2A expression (Sulaiman et al., 2010). SERCA 2A mediated uptake and release of calcium is pivotal to cardiac contraction and relaxation or in other words the systolic or diastolic function, and hence is a key target for therapeutic molecules. Therefore this finding is very important in explaining the resveratrol mediated improvement in systolic or diastolic function of the heart.

Oxidative stress and inflammation are cellular responses to stress. These two phenomena are highly involved in the genesis of heart disease and its progression to heart failure. Resveratrol is theoretically a weak antioxidant when compared to many other polyphenol compounds (Mikulski and Molski, 2010), while, its anti-inflammatory properties are well documented (Svajger and Jeras, 2012). Nuclear factor kappa B (NFkB) is a key transcription factor activated in response to cytokine and free radical levels in the cytosol. IkB is the protein that prevents the activation of NFkB in normal environments. Resveratrol treatment has been reported to prevent IkB degradation and inhibit NFkB activation (Shadfar et al., 2011), and translocation into the nucleus leading to the transcription of a variety of genes detrimental to the cell. At the same time resveratrol is also known to reduce levels of TNF alpha and IL-6 (Louis et al., 2012), two cytokines released by macrophages which can trigger NFkB activation. Resveratrol is reported to decrease iNOS expression (Hung et al., 2004) which is one of the genes transcribed by NFkB. Resveratrol treatment also upregulates key antioxidant enzymes like superoxide dismutase (Tanno et al., 2010), catalase (Movahed et al., 2012) and glutathione peroxidase (Xia et al., 2010) while reducing NADPH oxidase (NOX) expression (Xia et al., 2010). The transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) is a vital oxidative stress response inducer which binds to the antioxidant response element (ARE) and results in transcription of NADPH quinone oxidoreductase 1 (Nqo1), heme oxygenase-1 (HO-1) and other antioxidant genes. Resveratrol has been shown to promote Nrf2 activation in the heart (Hao et al., 2013). Taken together these multifaceted changes will help in reducing the generation of free radicals, while also increasing its eradication in pathological conditions. Accordingly, the antioxidant and anti-inflammatory properties of resveratrol are significantly contributing towards the prevention, attenuation or reversal of heart diseases in animals. Although antioxidant therapy has been unsuccessful in human clinical trials, resveratrol could be a potential candidate for future trials.

Another key mechanism involved in resveratrol mediated cardioprotection is its ability to downregulate proteins involved in cardiac fibrosis (Tanno et al., 2010). Fibroblast releases most of the profibrotic factors in the heart. However, not much has been reported in in vivo studies. Resveratrol has shown to reduce fibrosis in the heart associated with decrease in collagen expression levels. Tumor growth factor beta is a cytokine that stimulates fibrotic response in the heart. The ability of resveratrol to control TGF beta

Fig. 2. Molecular targets mediating resveratrol effects.

Molecular targets mediating resveratrol effects.
levels in heart might be a significant step in preventing fibrosis (Lin et al., 2008). Fibrosis results in stiffening of the heart muscle tissue resulting in diastolic abnormalities and to some extent systolic dysfunction too. Thus prevention of fibrosis with resveratrol might be help in preserving diastolic and systolic functions in heart disease.

Calcium channels play very important roles in maintaining the rhythm of heart beats and optimizing the cardiac output according to the demands of the body. However, in certain disease conditions, these channels function abnormally, resulting in irregular heart beats or arrhythmia. Resveratrol prevented arrhythmia in an animal model of heart disease and this was associated with the inhibition of L type calcium channels (Chen et al., 2008). This observation suggests that resveratrol treatment may be beneficial in preventing arrhythmias.

A significant amount of work on resveratrol mediated cardioprotection and associated mechanisms has been documented in the literature. Majority of this work has been done in in vitro models of heart disease, which is outside the scope of this review. However, a list of potential molecules that might be mediating resveratrol mediated cardioprotection as shown by in vitro studies is presented here (Fig. 2).

To summarize, resveratrol is a unique polyphenol because it has characteristics of a strong antioxidant and anti-inflammatory molecule, while it is also able to favorably regulate key cellular components to accelerate the healing process. A combination of these effects makes it much more effective and successful when compared to many other bioactive molecules that have been explored earlier.

**Resveratrol—interactions with drugs**

To date, only a few studies have examined the efficacy of resveratrol in combination with drugs, on cardiac structure and function in the settings of heart disease/failure. Thandapilly et al. reported that a combination of low dose resveratrol and a vasodilator proved to be better than either treatment alone in reversing hypertension and hypertension induced abnormalities in heart structure and function in the spontaneously hypertensive rat (Thandapilly et al., 2013). Similarly, Penumathsa et al. also reported superior cardioprotection with a combination of resveratrol and statin than either agent alone in hearts isolated from hypercholesterolemic rats which were subjected to myocardial ischemia–reperfusion (Penumathsa et al., 2007). A combination of resveratrol and insulin treatments was also reported by Huang et al. to improve diastolic heart function in type I diabetic rats, in comparison to resveratrol treatment alone. In the same study, Huang et al. also noted that when the hearts from type I diabetic rats were isolated and subjected to myocardial ischemia reperfusion, the resveratrol mediated improvement on systolic heart function was blunted when combined with insulin (Huang et al., 2010).

As mentioned in the earlier section (Resveratrol—Human clinical trials), in the human clinical trial conducted by Magyar et al. resveratrol was found to act synergistically with standard medication, and render added cardioprotection in patients with stable myocardial infarction (Magyar et al., 2012). As well, the clinical trials which examined cardiovascular risk factors also reported positive outcomes with combination of resveratrol with standard medication (Tome-Carneiro et al., 2012a,b, 2013a,b,c; Militaru et al., 2013).

Despite a favorable interaction observed in general between resveratrol and some clinically administered drugs, the number of studies examining such interactions is limited.

**Resveratrol—combination with exercise**

The beneficial effect of exercise on cardiovascular health is well documented (Perez-Terzic, 2012). Whether treatment with resveratrol would complement exercise has been a topic of a recent investigation. Dolinsky et al. (2012) reported that resveratrol not only complemented exercise, but also enhanced the beneficial effects of exercise on heart function in normal young rats. More recently, Dolinsky et al. (2013b) also compared the effects of resveratrol treatment with that of aerobic exercise in an animal model of cardiac dysfunction. Their results showed that resveratrol treatment was more effective than exercise training in improving cardiac function in doxorubicin exposed mice (Dolinsky et al., 2013b). Given these important observations, it would be of great interest to examine the combined effects of resveratrol and exercise in human subjects with cardiovascular disease or even heart failure. Unfortunately, very recent evidence casts some doubt on the notion that resveratrol treatment may complement exercise. In a clinical trial, Gliemann et al. reported that resveratrol blunted the beneficial effects of exercise on lowering blood pressure, and blood concentrations of several cardiovascular risk factors, in physically inactive aged men (Gliemann et al., 2013). Whether resveratrol would complement or blunt the beneficial effects of exercise on cardiovascular health in younger humans or in physically active humans of any age, remains to be explored.

**Resveratrol—combination with stem cells**

Stem cell based myocardial regenerative procedure is one of the emerging areas of research in the field of cardiovascular medicine; it often includes stem cell mobilization and transplantation (Singh et al., 2009). Resveratrol is one of the many compounds being extensively studied as a molecule which can enhance the mobilization of the embryonic-like stem cells (Wang et al., 2012). In a recent study conducted by Pinarli et al., treatment with resveratrol in conjunction with adipose-derived mesenchymal stem cell transplantation was more effective than mesenchymal stem cells alone in improving left ventricular developed pressure in rats exposed to doxorubicin (Pinarli et al., 2013). Delucchi et al. also evaluated the effect of resveratrol administration on cardiac progenitor cell pool and myocardial environment (Delucchi et al., 2012). The results from this study demonstrated that resveratrol treatment was effective in improving the functional abilities of both cardiac progenitor cell and the mature cardiac cells. Consequently, it prevented the unfavorable ventricular remodeling of the diabetic heart, leading to a marked recovery of ventricular function (Delucchi et al., 2012).

**Conclusions**

Despite significant strides made in resveratrol research in overall health and disease, there are important gaps which need to be addressed. These include improving strategies to increase bioavailability, and conduct long-term trials (animal and human) to assess the efficacy and toxicity of resveratrol. With specific regard to research on cardioprotection, there are fewer in vivo animal studies carried out in major cardiovascular diseases such as obesity and diabetes (both types I and II), unlike hypertension and ischemic heart disease, which has been reasonably well characterized. Similarly, there is a dearth of studies examining heart structure and function in patients with cardiovascular disease and overt heart failure. As well, research on the cardioprotective potential of resveratrol in combination with specific cardiovascular disease/heart failure drug or drugs as well as the potency of resveratrol versus specific drug or drugs, in cardiovascular disease/heart failure (in both animal and human studies) is limited. Similarly, the recent reports on beneficial effects observed with the combinations of resveratrol with exercise, and resveratrol with stem cells, in affording cardioprotection, are exciting, and need to be further explored.

More than a decade of research exploring the cardioprotective effects of resveratrol has yielded very promising results; only the future will determine whether indeed resveratrol will successfully translate from the laboratory to the bedside and become part of the standard regimen for patients with cardiovascular disease.

**Conflict of interest statement**

None.
References


