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The Cellular and Molecular Mechanisms involved in the Effects of Resveratrol on Cardiovascular Diseases

M. Hashemian (MD)[1], H. Zand (PhD)*[2]

1.Department of Nutrition and Biochemistry, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, I.R.Iran

2.Department of Cellular and Molecular Nutrition, Faculty of Nutrition, Shahid Beheshti University of Medical Sciences, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Resveratrol is a natural phytoalexin found in certain plants, such as red grapes. Several studies confirm the beneficial effects of resveratrol on the cardiovascular system. Similar to many other polyphenols, resveratrol initiates the intracellular pathways which are activated under energy constraints. This review aimed to investigate the effects of resveratrol on the cardiovascular health, focusing on the associated cellular and molecular mechanisms.

METHODS: In this study, we searched for English and Persian articles in PubMed and SID databases using keywords such as resveratrol, nitric oxide (NO), endothelial, cardiovascular diseases, oxidative stress, vascular inflammation, cardiac protection and polyphenol. Related articles were mostly published during 2002-2013.

FINDINGS: The initial survey of 72 collected articles indicated that resveratrol is able to neutralize oxidative species and activate Nrf2 while minimizing antioxidant damage. In addition, this compound enhances vascular function through increasing the production and bioavailability of NO in blood vessels via the stimulation of estrogen receptors. On the other hand, resveratrol, similar to calorie restriction, activates SIRT1 which is an NAD-dependent deacetylase. In addition, resveratrol exerts anti-inflammatory effects on blood vessels through NF-κB and inhibits platelet aggregation using NO. Resveratrol also provides cardiac protection against reperfusion injuries and is able to slow down the process of aortic and cardiac hypertrophy resulting in hypotension.

CONCLUSION: Resveratrol affects endothelial function, oxidative stress, vascular inflammation, platelet aggregation, hypertension, atherosclerosis and cardiac hypertrophy through a variety of mechanisms.

KEY WORDS: Resveratrol, Nitric Oxide, Endothelial, Cardiovascular Diseases, Oxidative Stress, Vascular Inflammation, Cardiac Protection, Polyphenol.

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***Corresponding Author: Hamid Zand (PhD)**
Address: Faculty of Food and Nutrition Research Institute, Farahzadi Boulevard, Shahrak Qods, Tehran, I.R.Iran.
Tel: +98 21 22357484
E-mail: hamidzand@gmail.com

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Introduction

Resveratrol, with the formula of trans-3, 5, 4′-trihydroxystilbene, is a natural phytoalexin polyphenol that protects plants against fungi. This substance exists in low concentrations in peels of red grapes, berries, peanuts, rhubarb roots and other herbs and plants (1). Prolonged exposure of grapes to UV radiation or storage in a cold place could result in the higher accumulation of this substance by 2-10 times (2). Although this substance has long been used in the Iranian traditional medicine for various treatments, resveratrol was first introduced in 1940 as a natural phenolic compound. However, it was neglected until the discovery of its inhibitory effects on cancer cells (3). Resveratrol is also the main polyphenol substance found in red wine (3). Some scholars believe that the reason behind the low incidence of myocardial infarction in France, despite the high intake of saturated fatty acids, is the regular consumption of red wine (the French paradox) (4). Discovery of the effects of French paradox draw the attention of many researchers to the protective mechanisms of red wine, especially the associated cardiovascular benefits.

On the other hand, advances in animal studies have revealed numerous medical benefits for resveratrol, including the inhibition of cancer, cardiovascular diseases, and ischemic damage, as well as the prevention of Alzheimer's disease (1). Furthermore, this substance has been shown to have many biological and pharmacological properties, including anti-atherosclerosis, anti-hypertensive, antioxidant and anti-inflammatory features. It can prevent cardiac reperfusion-induced damage and enhance blood vessel function as well.

Despite extensive research on cardiovascular diseases and the adjunctive therapies, these diseases are still the leading causes of mortality and morbidity across the world (5). Therefore, this review article aimed to investigate the effects of resveratrol on cardiovascular disorders. On the other hand, in order to translate the findings of animal studies into beneficial measures for humans, clinical safety should be considered paramount. This requires further attention to the pharmacological studies, as well as the metabolisms and molecular and cellular mechanisms of resveratrol.

This review article aimed to access the most recent findings regarding the effects of resveratrol on cardiovascular disorders, with emphasis on the molecular and cellular mechanisms of this natural substance.

Methods

In the current review, we searched for English and Persian articles in PubMed and SID databases using keywords such as resveratrol, nitric oxide, endothelial, cardiovascular diseases, oxidative stress, vascular inflammation, cardiac protection, and polyphenol. Related articles, which were mostly published during 2002-2013, were collected and investigated, and in order to increase the accuracy of the search, Mesh-based public keywords and their English equivalents were used. Initially, a list of titles and article abstracts existing in the databases was prepared, and the abstracts were examined in terms of thematic relation. Afterwards, the articles focusing on the molecular and cellular mechanisms and cardiovascular protective effects of resveratrol were closely studied. Studies conducted in other languages than English, those unrelated to the research question and studies that were biased towards the subject were excluded from this review. Only one researcher controlled the inclusion and exclusion criteria of the collected articles, and shorthand brief forms were designated in order to elicit data, including information on the subject, titles, names of the journals and authors, as well as on the mechanisms of resveratrol and the associated cardiovascular outcomes.

Result

In total, the term “resveratrol” was found in the titles, abstracts and keywords of 3087 articles in PubMed database. By limiting the articles to the ones related to cardiovascular diseases and molecular and cellular mechanisms, 772 and 72 articles were included, respectively. As for the SID database, there was only one research in relation to resveratrol, which mainly focused on the associated effects of the substance on the Parkinson’s disease. The obtained results of this study indicated that resveratrol, through a variety of mechanisms, applies therapeutic effects on several conditions such as oxidative stress, vascular inflammation, platelet aggregation, hypertension, atherosclerosis and cardiac hypertrophy.

Antioxidant Effects: One of the major features of resveratrol is the antioxidant properties, which seem to be caused by the increase in its internal sources of antioxidants rather than being directly involved in the collection of reactive oxygen species (ROS) (6). Resveratrol neutralizes ROS and other reactive species such as hydrogen peroxide, superoxide and hydroxyl

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radical preventing oxidative damage (7). Furthermore, resveratrol is able to increase the activity of all the three superoxide dismutase isoforms in endothelial cells, as well as the activities of catalase and glutathione peroxidase in the aorta and smooth cardiac-muscle cells (8). Moreover, it protects myocardial cells against ischemia-reperfusion injuries and oxidative stress (9, 10). In addition to neutralizing ROS, resveratrol reduces the production of these species. Nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase (NOX) is the most important enzyme which generates ROS in the cardiovascular system, and resveratrol decreases the expression and activity of this enzyme (1, 11). In one study, by blocking one of the kidney blood vessels of mice and inducing hypertension in them, resveratrol was observed to enhance the cardiovascular function through increasing the endogenous antioxidants and the inhibition of lipid peroxidation. Furthermore, it was able to repair the oxidative damage caused by hypertension in all the cells, including the cardiac muscle cells (12). For another thing, resveratrol is able to reduce the rate of ROS-induced cell death through initiating adenosine monophosphate-kinase (AMPK) activator in H9c2 cardiac cells (13). The activation of AMPK results in the conservation of the cellular energy, and therefore, it activates the catabolic pathways generating adenosine triphosphate (ATP), which is produced by mitochondrial and oxidative metabolism. In addition, AMPK activates SIRT1 (histone/ protein deacetylase sirtuin 1) through increasing the levels of cellular nicotinamide adenine nucleotides (NAD). Resveratrol causes the phosphorylation and activation of AMPK and subsequently, phosphorylates acetyl-CoA carboxylase, which leads to a reduction in lipid biosynthesis and an increase in fatty acid oxidation (14).

Nitric oxide: Resveratrol contributes to the expression of inducible nitric oxide (NO) synthase (iNOS) (15). Moreover, it increases the activity of NO in the endothelial cells through the following mechanisms: 1) stimulation of gene expression and increasing eNOS-mRNA stability (endothelial NO synthase) (16); 2) phosphorylation and deacetylation of eNOS binding to calmodulin using SIRT1 (18).

Moreover, through affecting the intracellular arginine and production of eNOS intracellular inhibitors (23), such as asymmetric dimethylarginine (ADMA), resveratrol increases the bioavailability of NO in blood vessels (24). Consequently, it improves vascular function by increasing the production of NO and its bioavailability in blood vessels (25) exerting antihypertensive, anti-platelet and anti-atherosclerotic effects (preventing the sticking of leukocytes and oxidation of low-density lipoprotein) while inhibiting vascular smooth muscle cell proliferation. Therefore, it could be inferred that the improvement of vascular function caused by resveratrol could be due to the increased production of NO and reduction of ROS. In a clinical trial, the acute administration of resveratrol (30, 90, 270 mg) resulted in the dilation of the brachial artery in patients with moderate, untreated hypertension (26).

Sirtuins: As mentioned above, the biological activity of resveratrol occurs through a variety of molecular mechanisms. Similar to other polyphenols, resveratrol initiates intracellular pathways which are activated during calorie restriction. These pathways are known to improve health and increase longevity in animals (27). One of the common features between resveratrol and calorie restriction is that they both activate SIRT1, an NAD-dependent deacetylase. In addition, resveratrol increases the expression of SIRT1 (28) and activates AMPK. By increasing the expression of NAD-producing enzymes and shifting the fuel source from carbohydrates to fat, AMPK makes more NAD available for SIRT1 (29), eventually leading to the activation of SIRT1.

The activity of SIRT1 depends on histones and is associated with various transcription factors such as P53, tumor protein 53, FOXO-family, and regulators of metabolism, transcriptional activators, peroxisome proliferators-activated receptor gamma (PPAR-γ) and proliferator-activated receptor gamma coactivator-1α (PGC-1α). Consequently, resveratrol improves mitochondrial activity and contributes to the gene expression for the oxidation of fatty acids (30). On the other hand, through expressing genes such as SIRT1, SIRT2 and SIRT4, as well as Foxo1 and Foxo3a, resveratrol prevents the reduction of cardiovascular functioning which occurs due to aging (e.g., cholesterol levels and inflammatory responses).

In addition, SIRT1 levels were observed to increase in a dose-dependent manner in the endothelial cells of patients treated by resveratrol. Resveratrol is known to impede aging in individuals exposed to H2O2 (31, 32). It also reduces cardiac apoptosis in mice caused by doxorubicin through P53 deacetylation using SIRT1 (33). However, the analysis of gene expression profile of heart suggests that many cardiovascular benefits resulting from the caloric restriction of resveratrol occur only when this substance reaches lower doses, in which it is still not able to activate SIRT1. Therefore, the

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assumption of resveratrol acting as a direct activator of SIRT1 needs to be further investigated (27).

The transcription factor Nrf2: Another mechanism of resveratrol in cardiac protection is to activate the nuclear factor 2, also known as NF-E2-related factor 2 (Nrf2). Nrf2 is a transcriptional factor arranging the coordination of mechanisms which neutralize ROS through binding to the antioxidant response element (ARE). In human coronary artery endothelial cells, resveratrol is known to increase the transcriptional activity of Nrf2, as well as the expression of genes regulated by ARE which are involved in the metabolism of free radicals (34). In addition, resveratrol significantly increases the expression of Nrf2 resulting in the improvement of cell survival and cardiac function tests (35).

Anti-inflammatory effects: Inflammation in coronary syndromes is of potential prognostic value; therefore, cardiologists have attempted to use a variety of combination treatments in order to reduce inflammatory markers after stroke (36, 37), and resveratrol is known to exert anti-inflammatory effects on blood vessels through the nuclear factor kappa B (NF-κB) (38). Furthermore, by decreasing the production of H2O2 (39), inhibition of IκB-kinase, and phosphorylation (40) and deacetylation of p65 (41), resveratrol is able to harness the production of NF-κB.

Platelet aggregation: For several years, anti-platelet drugs have been used to prevent myocardial infarction, and resveratrol has been shown to have anti-platelet aggregation properties. In addition, it is able to hinder platelet aggregation in patients resistant to aspirin (42). By producing and emitting NO to platelets, and also by stimulating guanylate cyclase which results in the production of cyclic guanosine monophosphate (cGMP), resveratrol is able to inhibit platelet aggregation (42). Moreover, resveratrol can directly increase the production of cGMP (43) and barrier the synthesis of thromboxane-A by the irreversible, non-competitive inhibition of cyclooxygenase-1 (44). At high concentrations, resveratrol causes platelet apoptosis and at lower concentrations, it can inhibit platelet activation using collagen (45, 46).

Resistance to ischemia (ischemic preconditioning): Other mechanisms in which resveratrol is involved include autophagy and ischemic preconditioning. Retrofitting or preconditioning is a process in which the heart encounters ischemia and reperfusion, and therefore, it becomes resistant to subsequent ischemia. After the occurrence of acute myocardial infarction, reperfusion with thrombolytic therapy or primary percutaneous coronary intervention is paramount for infarct size reduction. This condition is referred to as reperfusion injury and could affect the final size of the infarct tissue by up to 50% (47, 48). Resveratrol is known to provide cardiac protection against reperfusion injuries (49) while stimulating the process of ischemic preconditioning (4). Resveratrol exerts its effects on retrofitting through several mechanisms; for instance, it acts as a cardio-protective agent against apoptosis at lower doses in different routes, including SIRT1-FOXO1 pathways, or it can increase the expression of cell survival proteins, enhance ventricular recovery after ischemia and therefore, reduce myocardial infarction in size (50). Furthermore, it can increase NO and other antioxidant enzymes, inducing autophagy (15, 51), and improve myocardial ischemia by reducing oxidative stress and increasing vessel revascularization. Resveratrol can also cause the restoration of the miRNAs, which are expressed during ischemia and reperfusion (52). Concomitant use of γ-Tocotrienol and resveratrol is known to provide cardiac protection since both these combinations could synergistically increase survival signals through activating the survival pathways of Akt-Bcl2 (51). Moreover, feeding Longevinex (resveratrol with quercetin and rice bran phytate) to mice could reduce the myocardial infarct size and increase SIRT1 expression, which is associated with the induction of autophahy. Overall, Longevinex causes the phosphorylation and nuclear translocation of Foxo1, Foxo3a and Foxo4 which is indicative of the involvement of Foxo transcription factors in autophahy (53). Recently, researchers have claimed that resveratrol, similar to melatonin, could lead to the reduction of infarct size in mice's heart due to its saturation in red wine. However, that will not be effective if the mice have STAT3 deficiency or in case the tumor necrosis factor (TNF) receiver is destroyed. Consequently, it is suggestive of the fact that resveratrol applies its protective effects through initiating the signaling pathway of survivor activating factor enhancement (SAFE), which activates TNF and STAT3 (54).

Cardiovascular Hypertrophy: Several studies have proposed that resveratrol could slow down the process of aorta and cardiac hypertrophy (55, 56) by reducing the blood pressure, exerting anti-hypertrophic effects on AMPK signaling pathway and inhibiting Akt signaling pathway (57, 58). The recovery of cardiovascular remodeling in mice has been attributed to the anti-inflammatory and anti-fibrotic properties of resveratrol (59), which might occur without lowering the blood pressure (60). Furthermore, anti-hypertensive effects of resveratrol have been observed in animals, which are probably exerted through the inhibition of endothelin-1 synthesis and NO-induced vascular dilation (61, 62). In addition, resveratrol decreases the inhibition of phosphatidyl choline as well as muscle contraction (63).

Estrogen-like effects: Resveratrol shares structural similarities with estrogen. Estrogen applies its effects on

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the cardiovascular system through the activation of its receptors, which are able to alter gene transcription in the nucleus or activate the kinases to initiate signaling in the cytosol. In the same manner, resveratrol is able to activate both extra- and intracellular receptors of estrogen. Resveratrol immediately initiates the mitogen-activated protein kinase (MAPK) signaling pathway, initiating the phosphorylation of eNOS and production of NO (16). Moreover, it can increase NO production through binding to the estrogen receptors (64). Of course, resveratrol could increase the expression of eNOS via activating SIRT1 (65). One of the mechanisms through which estrogen is able to enhance cardiovascular health and reduce myocardial cell death is by activating eNOS (66). In addition, in the absence of tetrahydrobiopterin (BH4), which is a cofactor for eNOS, eNOS produces superoxide instead of NO. The production of BH4 lowers with age and during hypoglycemia; therefore, hypoglycemia impedes the process of ischemic preconditioning. GTP cyclohydrolase-1 is the main limiting enzyme in the synthesis of BH4. In mice, resveratrol increases the gene expression of GTP cyclohydrolase, and so, by increasing of BH4, it leads eNOS to prevailing of NO production (21). The heart has numerous estrogen α-dependent receptors, which induce a high metabolic activity and may lead to the adjustment of the genes associated with contraction, calcium homeostasis and membrane ATP binding (67).

The electronic and mechanical effects of resveratrol on the heart: According to several studies, resveratrol has a direct impact on cardiac cells. In an article, resveratrol was reported to reduce strength in the right atrial muscle fiber by 60% and decrease left ventricular muscle fiber by 20%, while also affecting the duration of intracellular action potentials. Furthermore, it has been indicated that in the presence of glyburide (K-ATP channel blocker), the changes induced by resveratrol may dramatically reduce (68). In a study by Liew et al., it was demonstrated that the acute administration of resveratrol could decrease the amplitude of calcium and increase the contraction curve of the cardiac cells, as well as some other cells, which is indicative of increased calcium sensitivity. Moreover, the timing of action potentials is known to decrease in a dose-dependent and time-dependent fashion. In these processes, the use of potassium channel blockers was not observed to have any effects on the functions of resveratrol, while the estrogen-receptor antagonist was found to diminish the effects of resveratrol (69). Such functions of resveratrol could justify its impact on arrhythmias as well. A summary of the effects of resveratrol on the cardiovascular system, along with the aforementioned mechanisms, is presented in table 1.

Table 1. Molecular mechanisms involved in the cardiovascular effects of resveratrol

Cardiovascular outcomes	Effects and mechanisms	Sources
Oxidative Stress Reduction	Increase of internal antioxidants	6, 8, 12
	ROS Neutralization	7
	Reduced expression of NOX (Decreased production of ROS)	11
	Increase of SIRT1 activity	29, 31
	Activation of Nrf2	34, 35
	Reduction of ROS-induced cell death through activation of AMPK	13
	Increased expression of eNOS	15
	Increased NOS mRNA stability	16
	eNos phosphorylation	17
	Estrogen-receptor stimulation	62, 64, 65
Improvement of endothelial function	eNos deacetylation binding to calmodulin by SIRT1	18, 29, 31
	eNos Reduction of eNos intracellular inhibitors	19
	Reduction of Caveolin 1 and its impact on eNos	20
	Increase of Tetrahydrobiopterin (BH4) and eNos lack of pair	21
	Increase of NO Bioavailability	23
	Increase of SIRT1activity	29, 31
Reduction of vascular inflammation	Reduction of NF-κB activity	39, 40
	Lack of NF-κB transcription	40
	Inactivation of NF-κB through deacetylation of p65	41
Inhibition of platelet aggregation	Increased amount and activity of NO	43
	Inhibition of thromboxane synthesis	44
	Apoptosis in platelets	45
	Inhibition of platelet activation by collagen	45
Cardiac preconditioning	Anti-apoptotic factor with different pathways, including SIRT1-FOXO1 pathways	50
	Induction of autophagy	51
	Restoration of miRNAs expressed during ischemia and reperfusion	52
Reduction of concentric cardiovascular hypertrophy	Hypotension	55
	Anti-hypertrophic effects of AMPK signaling pathway	56
	Inhibition of Akt signaling pathway	56
Hypotension	Inhibition of endothelin-1 synthesis	59, 60
	Vascular dilation induced by NO	59, 60
	Inhibition of Lysophosphatidylcholines and muscle contraction	61

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Side-effects of resveratrol: According to several studies, resveratrol has no adverse effects. However, a recent study demonstrated that resveratrol might lead to an increase in solid tumors and lymphomas (70). This is suggestive of the fact that resveratrol may also have pro-antioxidant effects, especially in the presence of copper which is known to increase in certain tumors. Therefore, the substance needs to be used with caution in case of human studies.

Discustion

According to the results of this study, resveratrol is considered an effective polyphenol in the improvement of cardiovascular disorders. It influences different mechanisms including endothelial function, oxidative stress, vascular inflammation, platelet aggregation, hypertension, atherosclerosis and cardiac hypertrophy. The antioxidant properties of resveratrol are among its most prominent features.

Furthermore, resveratrol reduces the production of ROS, increases the internal levels of antioxidant and collects active oxygen species. By increasing the production and bioavailability of NO, resveratrol can improve vascular functioning through its antihypertensive, anti-platelet, and anti-atherosclerosis agents. On the other hand, this polyphenol initiates intracellular pathways, which are activated during calorie restriction. In addition, resveratrol significantly increases the expression of Nrf2 causing synchronization mechanisms to neutralize ROS, while applying anti-inflammatory effects on the vascular system using NF-κB. Resveratrol causes the inhibition of NF-κB by reducing the production of H2O2, inhibition of NF-κB kinase, and phosphorylation and deacetylation of p65. Furthermore, it inhibits the synthesis of thromboxane and exerts anti-platelet effects by increasing the production of NO and cGMP, as well as the irreversible, non-competitive inhibition of cyclooxygenase-1. At high concentrations, resveratrol is able to cause platelet apoptosis while at lower concentrations, it can inhibit platelet activation using collagen (49). Moreover, resveratrol is known to stimulate the process of ischemic preconditioning.

Due to the reduction of blood pressure, the anti-hypertrophic effects of AMPK signaling pathway and the inhibition of Akt signaling pathway, this compound is able to slow down the process of cardiac hypertrophy. In addition, resveratrol exerts anti-hypertensive effects through such mechanisms as inhibition of endothelin-1 synthesis, NO-induced dilation of blood vessels and the inhibition of muscle contractions. Moreover, it can activate the extra- and intracellular receptors of estrogen. Resveratrol could immediately activate the MAPK signaling pathway, and initiate the phosphorylation of eNOS as well as the production of NO. Furthermore, it can increase the production of NO through binding to estrogen receptors, and even though it may affect the duration of action potentials, it preserves its anti-arrhythmic properties.

Despite the fact that several studies have investigated the effects of resveratrol on animals, human studies in this area are scarce and they have mostly been conducted on cultured cells. Therefore, further clinical trials in this regard are required in order to assess the exact effects of this substance on humans, with regard to the recommended dosage, and the time and duration of administration.

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