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Review Article

Potential of Resveratrol in Cardiovascular Disorders – A Systematic Review

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ABSTRACT

Background and Objectives: Cardiovascular diseases (CVDs) are the leading cause of global mortality, responsible for 17.9 million deaths annually. Antioxidants like resveratrol (RES), a polyphenolic compound found in grapes and red wine, have gained attention for their potential cardioprotective effects. This review synthesizes existing research on resveratrol's impact on various cardiovascular conditions, including atherosclerosis, coronary artery disease (CAD), hypertension, cardiac remodeling, stroke, myocardial ischemia, heart failure, and Chagas heart disease.

Materials and Methods: A systematic review was conducted, analyzing studies from January 1991 to August 2024. Databases searched included PubMed, Scopus, and Web of Science, focusing on randomized controlled trials, meta-analyses, and systematic reviews involving both human and animal subjects. Data were extracted on study design, treatment protocols, cardiovascular outcomes, and adverse effects.

Results: Resveratrol exhibits significant cardioprotective effects, primarily through its antioxidant and anti-inflammatory properties. It reduces oxidative stress, mitigates endothelial dysfunction, and decreases inflammation, contributing to the prevention and management of atherosclerosis, CAD, hypertension, and myocardial ischemia. Additionally, resveratrol shows promise in improving stroke outcomes, enhancing cardiac function in heart failure, and managing Chagas heart disease. However, bioavailability challenges remain a barrier to its therapeutic efficacy.

Conclusions: Resveratrol holds promise as a natural therapeutic agent for various cardiovascular diseases. While preclinical evidence is strong, more large-scale human trials are needed to confirm its clinical applicability. Addressing bioavailability issues could further enhance its potential as a treatment option in cardiovascular care.

Keywords: Resveratrol, Atherosclerosis, Coronary artery disease

Highlights

- Resveratrol has been shown to lower LDL cholesterol and triglycerides while increasing HDL cholesterol
- Resveratrol promotes nitric oxide (NO) production, leading to vasodilation and reduced blood pressure.
- Resveratrol has shown promise in reducing cardiac fibrosis, inhibiting ventricular hypertrophy, and improving overall cardiac function
- Resveratrol offers potential therapeutic benefits for ischemic stroke patients by reducing inflammation, promoting neurogenesis and angiogenesis.
- Resveratrol has been effective in reducing oxidative stress and improving cardiac function in Chagas heart disease.

Introduction

Cardiovascular disease (CVD) refers to diseases affecting the heart and circulatory system, including conditions such as coronary artery disease, heart failure, stroke, arrhythmias, and peripheral artery disease. CVDs are a major global health issue, responsible for approximately 17.9 million deaths annually, accounting for

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32% of all global fatalities (1). The global economic burden of CVD exceeds $1 trillion, with costs related to healthcare, lost productivity, and premature death (1). In the United States, the Centers for Disease Control and Prevention (CDC) reports about 697,000 deaths from CVD each year (2). Approximately 47% of American adults have at least one of three key risk factors: high blood pressure, high cholesterol, or smoking (2). The rapid rise of these diseases is driven by numerous factors, including a growing elderly population, unhealthy lifestyle habits, excessive smoking and alcohol use, socioeconomic status, and genetics (3).

Antioxidants have emerged as a promising strategy for managing CVDs, primarily due to their ability to counteract oxidative stress by neutralizing the effects of damaging free radicals (4). Oxidative stress plays a vital role in the progression of CVDs by exacerbating endothelial and smooth muscle dysfunction and amplifying risk factors such as atherosclerosis (4). Furthermore, antioxidants protect against CVDs by preventing low-density lipoprotein (LDL) oxidation, modulating inflammation, and enhancing overall vascular health (4). Among these antioxidants, resveratrol (RES)—a polyphenolic compound found in sources like red wine and grapes—has gained significant attention for its potential cardiovascular benefits (5). In addition to its antioxidant and anti-inflammatory properties, RES offers protection against CVDs through various other mechanisms. These include promoting the production of nitric oxide (NO), lowering LDL cholesterol and triglycerides while increasing high-density lipoprotein (HDL) cholesterol, inhibiting platelet aggregation and blood clot formation, modulating cardiac hypertrophy and fibrosis, improving insulin sensitivity and glucose metabolism, reducing blood pressure, and activating proteins involved in cellular stress resistance and metabolic regulation, namely sirtuin 1 (SIRT1) (6,7,8). RES's multifaceted effects on cardiovascular health underscore its potential as a beneficial agent in the management of CVDs.

Ongoing studies continue to evaluate RES's therapeutic value in treating cardiovascular illnesses. These findings focus on RES's direct and indirect influence on CVD risk factors and conditions such as atherosclerosis, hypertension, stroke, myocardial ischemia, heart failure, viral infections, and more. This review aims to contribute to the existing body of evidence by providing a comprehensive and up-to-date synthesis of research on the cardiovascular benefits of resveratrol (RES). While previous studies have explored specific aspects of RES's effects on cardiovascular health, this review seeks to integrate findings across a wide range of cardiovascular conditions, including atherosclerosis, coronary artery disease, hypertension, cardiac remodeling, stroke, myocardial ischemia, heart failure, and Chagas heart disease.

Materials and Methods

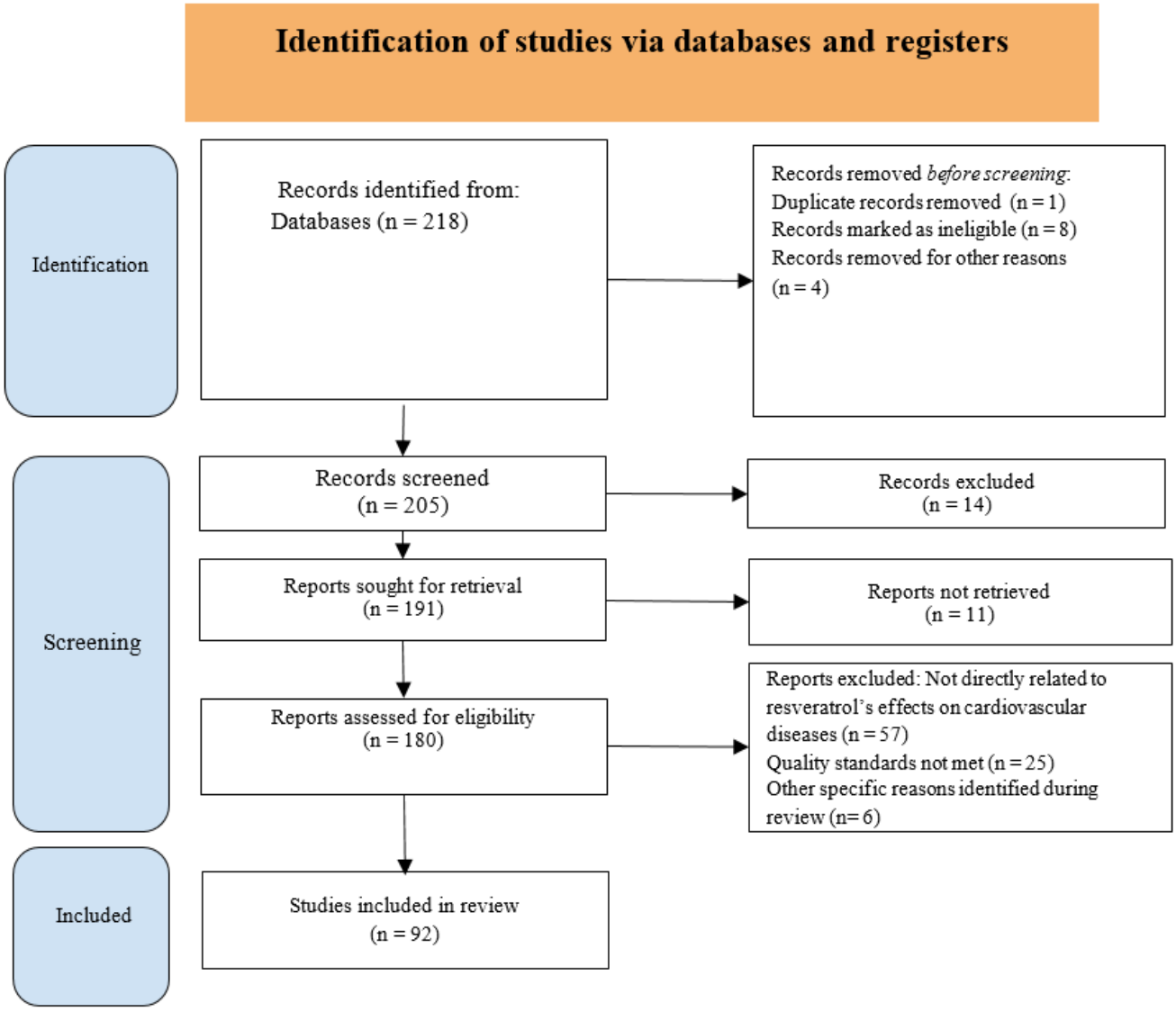
This review systematically examines the role of resveratrol in cardiovascular health, focusing on research published from 1991 onward. It includes a range of study types such as randomized controlled trials (RCTs), meta-analyses, and systematic reviews to provide a comprehensive understanding of resveratrol's effects on cardiovascular diseases.

Search Strategy: A detailed search was conducted using databases such as PubMed, Scopus, and Web of Science. Keywords included "resveratrol," "cardiovascular diseases," "myocardial ischemia," "heart failure," and "oxidative stress." The search was confined to articles published between January 1991 to August 2024.

Inclusion Criteria: Studies were selected based on their evaluation of resveratrol's impact on cardiovascular health, involving either human or animal subjects, and published in peer-reviewed journals. This included basic research, clinical trials, and observational studies.

Exclusion Criteria: Studies were excluded if they were not directly related to resveratrol's effects on cardiovascular diseases, including reviews and editorials. Articles lacking relevance to the review's focus or failing to meet quality standards were also omitted.

Data Extraction and Analysis: Information was extracted regarding study design, sample size, treatment protocols, cardiovascular outcomes, and adverse effects. The quality of studies was assessed using appropriate tools, and findings were synthesized to offer an overview of resveratrol's efficacy.



Study selection flow chart

Below is Table 1 Summary of Resveratrol's clinical effects. This will be used to reference information on figures.

Bioavailability of Resveratrol

The bioavailability of a drug is strongly correlated with its therapeutic value. Factors such as solubility and metabolism impact the bioavailability of resveratrol (5). When resveratrol is administered orally, it is absorbed from the gastrointestinal tract and enters portal circulation, where it is partially metabolized by the liver (5). This process leads to the formation of key metabolites, including resveratrol-3-O-sulfate and resveratrol-4'-O-sulfate (6). The rate at which these metabolites are formed affects the concentration of unmetabolized resveratrol that enters systemic circulation. Oral absorption of resveratrol is relatively high at 75% (7).

Table 1. Summary of Resveratrol's clinical effects

Species	Year	Type	Duration	Aim	Results
Human	2021	Review	N/A	Gender Differences in Atherosclerotic Vascular Disease	Men have a higher rate of atherosclerosis and plaque rupture compared to women due to the cardioprotective effects of estrogen
Rodent	2011	RCT	80 days	resveratrol's influence CD40 ligand (CD40L) and its receptor CD40 in platelets of hypercholesterolemic	lower triglyceride and LDL levels as well as increase HDL levels

Species	Year	Type	Duration	Aim	Results
Porcine artery	2006	In vivo	20 minutes	Resveratrol effect on artery	Vasodilatation Induced by Resveratrol in Isolated Porcine Coronary Artery
Human	2012	RCT	3 months	If resveratrol had a clinically measurable cardioprotective effect in patients after myocardial infarction.	patients had improved left ventricle diastolic function, endothelial function, and lower LDL-cholesterol levels in 3 months, compared to controls
Humans	2019	Meta-Analysis	N/A	To analyze the effect of resveratrol on BP.	In conclusion, long-term resveratrol supplementation may significantly improve blood pressure by lowering DBP more than SBP
Rodent	2020	RCT	4 weeks	Test the effect of resveratrol on the blood pressure of normal pregnant rats and pregnant rats with high salt intake.	Resveratrol has antihypertensive effects rats with high salt intake.
Rodent	2021	RCT	4 weeks	Does Resveratrol effect Cardiac Remodeling	Resveratrol Ameliorates Cardiac Remodeling in a Murine Model of Heart Failure With Preserved Ejection Fraction
Human	2016	RCT	1 year	Test if Resveratrol improves outcomes for patients with delayed r-tPA treatments.	Resveratrol attenuates the up-regulation of MMPs and extends the therapeutic window of r-tPA providing a more efficient treatment for ischemic strokes.
Rodent	2015	Meta-Analysis	N/A	Test if Resveratrol can repair microglial cells after an ischemic stroke.	Resveratrol has been shown to promote neurogenesis by increasing growth factors such as FGF and NGF and significantly increasing the expression rates of neuronal markers with bromodeoxyuridine.
Rodent	2019	Meta-analysis	N/A	Investigate the effects of preconditioning with resveratrol on myocardial ischemia and reperfusion injury	Preconditioning with resveratrol provided a favorable impact in preventing myocardial ischemia and reperfusion injury
Human	2021	Systematic Review	N/A	Evaluate the evidence for resveratrol as both a preventative measure and treatment in the context of cardiovascular disease, myocardial ischemia and heart failure	Resveratrol has a cardioprotective role in the prevention and treatment of ischemic heart disease and heart failure
Human	2020	RCT	3 months	Evaluate evidence of the positive influence of resveratrol on heart failure.	Decreased leukocyte activity may be a key mechanism of resveratrol, leading to its cardioprotective benefits in heart failure.
Rodent	2018	ECT	2 weeks	Investigate whether resveratrol could improve MI-induced cardiac remodeling and HF in rats through the inhibition of CYP1B1 and its metabolites.	Resveratrol therapy significantly improved ejection fraction and decreased postinfarction left ventricular and atrial remodeling.
Rodent	2016	RCT	60 days	Resveratrol effect on Mice heart exposed to Trypanosoma Cruzi	exposed mice had decreased prolonged PR and QTc intervals, elevated heart rates, and corrected sinus arrhythmia

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However, the bioavailability of resveratrol can be significantly impacted by the presence of certain macro- and micronutrients in the diet. These include:

- **Dietary Fats** : While fats can enhance the absorption of some lipophilic compounds, in the case of resveratrol, a high-fat meal can increase the rate of metabolism and clearance, thereby reducing its bioavailability. **Management**: To mitigate this, it may be beneficial to take resveratrol with a low-fat meal to avoid rapid metabolism and clearance from the body (7).
- **Proteins**: Certain proteins and amino acids can bind to resveratrol, forming complexes that are less readily absorbed in the gastrointestinal tract. **Management**: It's advisable to avoid high-protein meals around the time of resveratrol intake to reduce the potential for these interactions (7).
- **Polyphenols**: Other polyphenols, such as those found in tea, coffee, and some fruits, can compete with resveratrol for absorption and metabolic pathways, decreasing its bioavailability.
- **Management**: Limiting the consumption of other polyphenol-rich foods and beverages close to the time of resveratrol supplementation can help improve absorption (7).
- **Minerals**: Micronutrients like iron and calcium can form insoluble complexes with resveratrol, particularly when taken in high amounts, reducing its absorption. **Management**: Avoiding the simultaneous intake of high-calcium or iron-rich foods or supplements with resveratrol can enhance its bioavailability (7).

Many studies struggle to replicate the positive effects of resveratrol in vivo compared to in vitro, likely due to challenges associated with its bioavailability (5). To address this issue, several techniques have been investigated. Nanotechnology-based approaches and micronization techniques have demonstrated potential in enhancing resveratrol's absorption. By using nanocarriers such as micelles, polymers, carbon-based materials, and liposomes, researchers were able to deliver resveratrol to specific sites in the body that would not typically be accessible due to their small size (7). This site-specific form of drug delivery provides a significant therapeutic advantage by reducing resveratrol's harmful side effects on the body (7).

Resveratrol Safety Profile

In a pharmacokinetic research study, four cohorts of 10 individuals were established for experimentation with resveratrol. Out of each cohort, eight individuals were subjected to increasing doses of trans-resveratrol (25, 50, 100, or 150 grams), while two individuals received a placebo. Each participant received treatment or a placebo six times daily for a total of thirteen doses. The investigation documented a total of 18 adverse reactions, of which only nine adverse events were deemed potentially linked to the treatment. A recurrent frontal lobe headache, observed in only one individual spanning the 25, 50, and 150 mg dose groups, highlighted the mild nature of the reported adverse reactions. All adverse events were categorized as no more than mild, leading the investigators to establish the tolerability of trans-resveratrol, irrespective of dosage (9).

Another study involved 40 healthy volunteers (18 male and 22 female) who were administered a single dose of resveratrol at 0.5, 1.0, 2.5, or 5.0 grams. Subsequent follow-ups with the participants revealed an absence of serious reactions. 57.5% of the participants, spanning all four dosage groups, reported minor adverse reactions. Potential drug-related effects, specifically an increase in bilirubin and alanine aminotransferase levels, were documented in 5% of the volunteers from the 1.0-gram dosage group. However, each participant experienced only one of these symptoms, with the observed events subsiding within seven days following the four days of drug administration (8).

These studies suggest that resveratrol holds promise as a potential therapeutic agent, supported by a safety profile characterized by mild and transient adverse events. The findings contribute to the evolving discourse on the prospective role of resveratrol in therapeutic applications, emphasizing the need for further investigation and validation.

Results

Resveratrol for the Treatment of Atherosclerotic Effects

Atherosclerosis is a chronic inflammatory disorder characterized by the accumulation of fatty plaques in the blood vessels, followed by smooth muscle cell proliferation and inflammation (10,11). This narrowing of the blood vessel lumen leads to clinical manifestations such as strokes, coronary artery disease (CAD), and peripheral arterial disease (PAD) (12). Atherosclerosis is implicated in nearly 50% of all deaths in developed countries (10). About 75% of acute myocardial events are attributed to plaque rupture, underscoring the condition's severity. Men have a higher rate of atherosclerosis and plaque rupture compared to women, largely due to the cardioprotective effects of estrogen (13,14). Risk factors for atherosclerosis include hypercholesterolemia, age over 45 in men, age over 55 in women, cigarette smoking, obesity, diabetes mellitus, low HDL, and hypertension (15,16,17).

A study conducted by Göçmen et al. examined resveratrol's effect on triglyceride and LDL levels in rats, demonstrating resveratrol's ability to lower triglyceride and LDL levels while increasing HDL levels (18).

Another study investigated resveratrol's effects on HMG-CoA reductase, an enzyme involved in cholesterol formation, in hamsters (19,20). The study found a significant decrease in HMG-CoA reductase levels in hamsters treated with resveratrol compared to the control group (19). This suggests the potential for incorporating resveratrol with drugs that function as HMG-CoA reductase inhibitors, such as statins.

Research has also shown resveratrol's capacity to increase LDL receptors in vivo in hepatocytes (21). Additionally, studies highlight its potential in reducing the oxidation of LDL, a critical step in the formation of fatty plaques and the pathogenesis of atherosclerosis (22,23). This is illustrated in Figure 2. Previous studies have demonstrated resveratrol's ability to inhibit foam cell generation, another crucial step in the formation of fatty plaques, by decreasing NADPH oxidase levels in macrophages and reducing MCP-1 (24). Resveratrol may also decrease the proliferation of smooth muscle cells (25). By reducing atherosclerosis, resveratrol can serve as a preventative measure against the conditions caused by this disease.

Resveratrol also addresses the inflammation that plays a major role in atherosclerosis. It has been shown to decrease TNFα levels, NF-κB activation, and the expression of adhesion proteins such as ICAM-1 and VCAM-1 (26,27). Additionally, through the modulation of miRNAs, resveratrol can reduce pro-inflammatory cytokines while increasing anti-inflammatory cytokine production (28).

Resveratrol for the Treatment of Coronary Artery Disease

Coronary artery disease (CAD) is a condition related to atherosclerosis, characterized by plaque that occludes a coronary vessel, obstructs blood flow, and leads to a decrease in the delivery of nutrients and oxygen to the myocardium (29). This condition is the leading cause of death worldwide (30). CAD accounts for more than 2% of the global burden of disease and over 32% of all cardiovascular diseases (29). The risk factors implicated in CAD are the same as those for atherosclerosis, as mentioned in the previous section.

Resveratrol has shown promise in addressing CAD. In post-myocardial infarction (MI) patients, those treated with resveratrol showed improved left ventricular diastolic function, enhanced endothelial function, and lower LDL-cholesterol levels within three months compared to controls (31). In a recent study, clinically diagnosed individuals with CAD taking resveratrol had significantly higher HDL levels compared to control groups (32). Resveratrol has also demonstrated antioxidant, anti-inflammatory, and anti-proliferative properties specifically concerning coronary arteries in several studies (33,34,35). One mechanism of resveratrol's anti-proliferative ability was reported by El-Mowafy et al.

Using porcine coronary arteries, the study revealed that samples treated with resveratrol had lower MAPK 25 activity, which is implicated in the proliferation of smooth muscle cells (36). Another study highlighted resveratrol's ability to dilate porcine coronary arteries (37). The study demonstrated increased cyclic guanosine monophosphate (cGMP) levels in samples treated with resveratrol, and the increased cGMP was correlated with vasodilation (38,39). Resveratrol has also been shown to lower platelet aggregation, a pathological feature in both atherosclerosis and CAD (40,41,42). All these studies suggest a preventive role for resveratrol in the management of CAD.

Resveratrol for the Treatment of Hypertension

Hypertension guidelines have evolved over the years. The most current classification defines normal blood pressure as systolic and diastolic readings of less than 120/80 mmHg. The following chart displays the updated blood pressure measurements required to diagnose stage 1 and stage 2 hypertension, as well as a hypertensive crisis (43). Individuals who lead an unhealthy lifestyle are at a higher risk of developing hypertension. Risk factors include smoking, a sedentary lifestyle, and an unhealthy diet. Hypertension is considered a major cause of heart disease, stroke, and the second most common cause of chronic kidney disease (43).

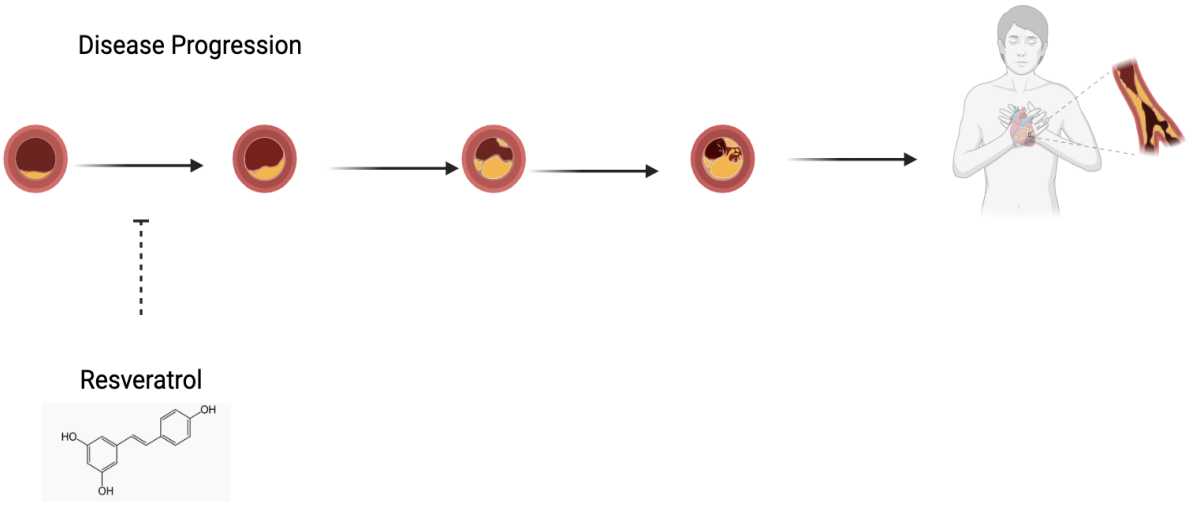

Figure 1 . Resveratrol inhibition of Atherosclerosis. Studies from the figure 2 are cited in Table 1. Created with Biorender.com

Resveratrol has been proven to have antihypertensive effects by increasing endothelial cell production of nitric oxide (NO), a potent vasodilator. NO activates guanylyl cyclase, leading to the formation of cyclic guanosine monophosphate (cGMP), which causes vasodilation by dephosphorylating the myosin light chain complex and inactivating smooth muscle constriction (44). An additional beneficial effect of resveratrol is produced by activating AMPK, which leads to the downregulation of ras-related C3 botulinum toxin substrate 1 (Rac1). Rac1 functions by increasing reactive oxygen species levels, thereby raising blood pressure. Studies in mouse models have demonstrated resveratrol's sequence of events leading to the inhibition of Rac1 and a reduction in blood pressure levels (45). Regarding the morphological changes caused by hypertension, a recent study on rats treated with resveratrol revealed its ability to prevent the atrophy of endothelial cells, tunica media, and smooth muscle cells of the aorta (46). This can help prevent the development of several clinical manifestations of hypertension, such as aortic dissection.

Resveratrol also helps prevent hypertension through its action on the kidneys, where it increases salt excretion without affecting the glomerular filtration rate (GFR). Its direct effect on renal tubules' handling of sodium can help prevent an increase in serum sodium levels, a key factor in causing hypertension (47). In a meta-analysis conducted by Fogacci et al., the effects of resveratrol supplementation on blood pressure (BP) were assessed through a review of studies in which resveratrol was administered to humans over an extended period. The results indicated that this supplementation may significantly improve BP over time, primarily by impacting diastolic blood pressure (DBP) more than systolic blood pressure (SBP) (48).

Resveratrol for the Treatment of Cardiac Remodeling

Cardiac remodeling (CR) is defined as a group of cellular or molecular changes in the heart, such as alterations in the mass or size of the valves, ventricles, and atria (49). These changes typically manifest after cardiac injury from various origins. CR results in a poor prognosis due to its association with ventricular dysfunction and arrhythmias (49).

Zheng et al. explored the effects of resveratrol on cardiac remodeling due to hypertension. In the study, the experimental group showed a decrease in left atrial size and a reduction in cardiac biomarkers, including pro-collagen type I C-peptide and galectin-3, which indicate cardiac fibrosis (50). Resveratrol also improved ventricular dysfunction, although it did not alter ventricular structure (50). Another study examined the effects of resveratrol on cardiac remodeling in mice with heart failure with preserved ejection fraction (HFpEF). The mice with HFpEF developed left ventricular hypertrophy, diastolic dysfunction, and pulmonary congestion (52). They also exhibited increased type 1 and type 3 collagen and TGF-B mRNA expressions, leading to cardiac remodeling and fibrosis (52). TGF-B mRNA expression is upregulated through the Smad 3 signaling pathway. Mice treated with resveratrol showed significantly decreased Smad 3 transcriptional activity due to Sirt1 activation (52). Another study demonstrated that resveratrol use in rats after myocardial infarction improved cardiac function and left ventricular function (53). The study found that resveratrol decreased inflammatory cytokine levels, leading to reduced fibrosis (53).

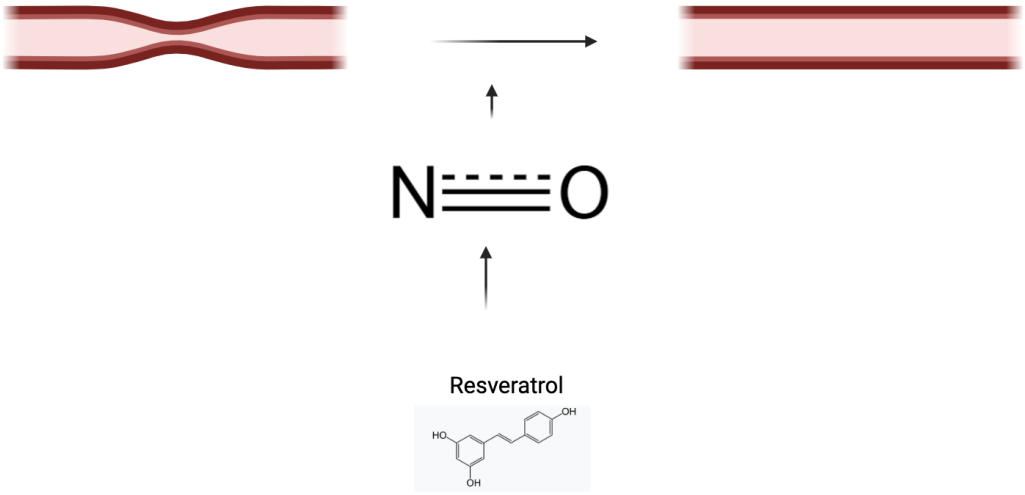

Figure 2 . Resveratrol antihypertensive effects through the increase in nitric oxide (NO). Studies from the figure 2 are cited in Table 1. Created with Biorender.com

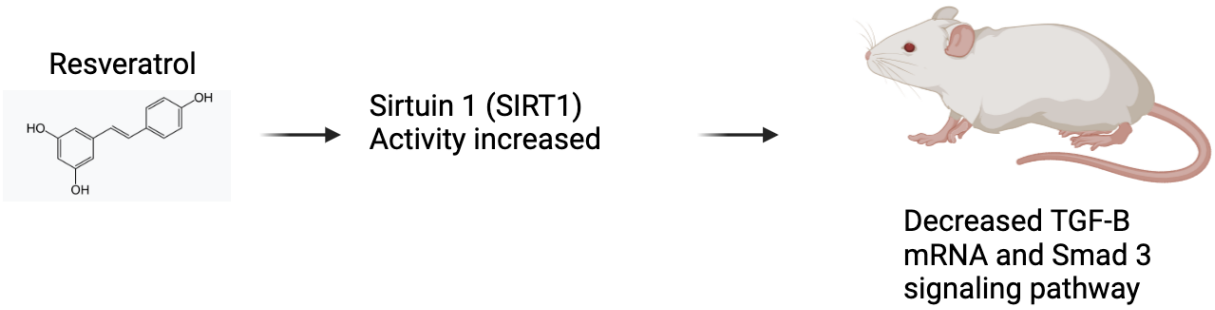

Figure 3 . Resveratrol effects through Sirtuin 1 (SIRT1) on Cardiac Remodeling. Studies from the figure 4 are cited in Table 1. Created with Biorender.com

Resveratrol for Stroke

Strokes represent a significant complication arising from various dysfunctions within the body. Ischemic strokes result from obstructed cerebral arteries caused by thrombus formation, emboli, or atherosclerosis (54). The current treatment for ischemic stroke, which constitutes the majority of strokes, is not very efficient. It includes reperfusion with recombinant tissue plasminogen activator (r-tPA) via intravenous administration within 4.5 hours of onset, and only 5% of patients are eligible (54). Neuronal cell death in strokes can occur due to several mechanisms, including apoptosis, necrosis, inflammation, and protein misfolding.

Due to the complex nature of strokes and their treatment, researchers have been exploring alternative options. In a meta-analysis by Liu et al., resveratrol was found to have a neuroprotective role in ischemic stroke in rodents. There are multiple mechanisms by which resveratrol can be used as therapy for ischemic stroke, including its anti-inflammatory properties, promotion of angiogenesis and neurogenesis, improvement of metabolism and edema, and antioxidant activity in microglial cells (55).

Resveratrol has been shown to promote neurogenesis by increasing growth factors such as FGF and NGF, thereby repairing the damage caused by ischemic strokes (55). The treatment also significantly increased the expression rates of neuronal markers, as evidenced by bromodeoxyuridine incorporation in the ischemic lesion site, promoting the growth of new cells (55).

Resveratrol's anti-inflammatory effects help block secondary brain damage following ischemic and traumatic injuries to the brain (56). It inhibits the release of the pro-inflammatory cytokine IL-6, which is released during hypoxic episodes in glial cells. Cytokines are chemical messengers that signal various cascades and have effects on other cells.

Resveratrol also activates SIRT1 and PPAR, both of which inhibit the nuclear translocation of nuclear factor kappa B (NF-κB) signaling, a key mediator of inflammation (56). When the body encounters a sub-lethal ischemic insult, it prepares the organ for a more severe insult, leading to a type of protection known as ischemic preconditioning (IPC). Resveratrol has been shown to induce IPC in hippocampal cultures and confer tolerance against global cerebral ischemia through its interaction with SIRT1 (56).

Resveratrol can also have a preventative effect on patients at risk of recurrent strokes due to its effects on the blood-brain barrier. Treatment reduces blood-brain barrier disruption and edema following a stroke without affecting regional cerebral blood flow (57). This is achieved by preventing the transcription of TNFα, IL-1β, and MMP-9, leading to decreased edema and improving recovery chances (56).

Resveratrol treatment also helps reduce markers of oxidative stress, such as ROS, thereby preventing neuronal cell death associated with strokes. The treatment protects endothelial cells, resulting in improved viability against oxygen and glucose deprivation seen in microglial cells during a stroke (57).

Delaying r-tPA treatment has been shown to increase the levels of MMPs, which can destroy the extracellular matrix of cells. Resveratrol decreases MMP levels in humans and strengthens the blood-brain barrier (58). In a clinical trial conducted by Chen et al., patients who had suffered a stroke with a clearly defined time of onset were treated with resveratrol along with r-tPA. The study showed that resveratrol improved outcomes for patients receiving delayed r-tPA treatment (58). Therefore, resveratrol attenuates the upregulation of MMPs and extends the therapeutic window of r-tPA, providing physicians with a more effective treatment option for patients affected by ischemic stroke.

Resveratrol Treatment of Myocardial Ischemia

Myocardial ischemia is a complex pathophysiological process defined by a mismatch between the supply and demand of oxygen in cardiac tissue (59). The mechanisms behind this mismatch are highly variable and interdependent, with the main contributors including atherosclerosis, vasospasm, inflammation, and coronary microvascular dysfunction (60). In adequately perfused resting cardiac tissue, oxidative phosphorylation is responsible for more than 90% of cardiac ATP production, which is maintained by oxygen consumption ranging from 60 to 150 microliters/gram/min (61). Once oxygen consumption becomes insufficient to sustain oxidative phosphorylation, cardiac myocytes rely on anaerobic glycolysis to produce the minimal amount of ATP required for survival (62). If hypoperfusion is sustained, it results in mitochondrial dysfunction and cell lysis, leading to irreversible structural and functional damage (63). Early reperfusion of ischemic tissue through percutaneous

coronary intervention (PCI) is associated with better restoration of blood flow, lower 30-day recurrence, and lower 30-day mortality rates following a myocardial infarction (64). However, reperfusion in the setting of acute coronary syndromes may carry its own risks, as it is associated with an acute increase in ROS production and intracellular calcium concentration, which elicits myocardial damage through the opening of mitochondrial permeability transition pores (65).

Resveratrol has been proposed as a treatment for reperfusion injury due to its potent antioxidant and anti-mitochondrial dysfunction properties. A meta-analysis by Mao et al. investigated the effect of resveratrol on myocardial reperfusion injury in animal models. Resveratrol was found to suppress myocardial inflammation through the inactivation of the NALP3 inflammasome and the TLR4/NF-κB pathway. Additionally, resveratrol protects against myocyte apoptosis by suppressing ROS production and subsequently inhibiting mPTP opening (66). Another study found similar results in their research on resveratrol therapy in 90 male rats with surgically induced myocardial injury. The study highlighted decreased serum inflammatory markers such as IL-1β, TNF-α, and IL-6, as well as decreased myocardial injury markers such as CK-MB and LDH (67). A systematic review of animal and human trials also found a positive effect of resveratrol in protecting against cardiac damage secondary to atherosclerosis, heart failure, and myocardial infarction. Animal models of ischemia/reperfusion injury within the review show that a longer duration of pre-treatment with resveratrol may reduce infarct size and promote more rapid recovery of cardiac function (68). This suggests a potential role for resveratrol in preventing severe outcomes in patients at risk for developing myocardial ischemia.

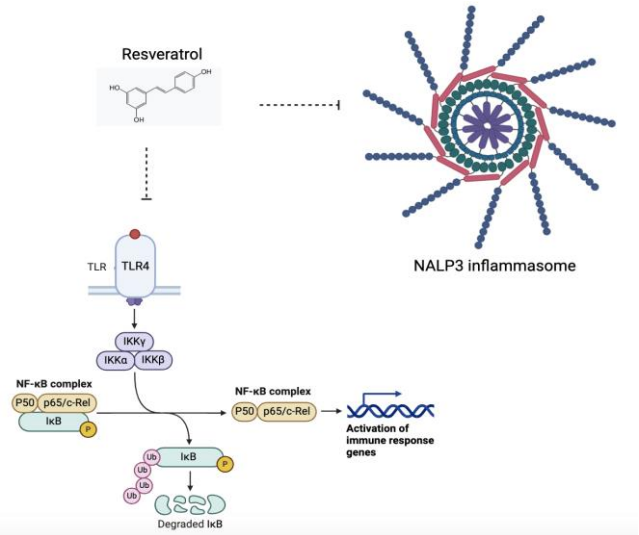

Figure 4 . Resveratrol suppressing NALP3 inflammasome and the TLR4/NF-kB pathway. Studies from the figure 3 are cited in Table 1. Created with Biorender.com

Resveratrol Treatment of Heart Failure

Heart failure is a chronic circulatory illness defined by the heart's inability to properly pump blood, resulting in insufficient perfusion of essential organs and tissues (69). This condition is frequently caused by structural or functional cardiac problems, such as myocardial infarction, hypertension, or valvular heart disease (70). Symptoms of heart failure include fatigue, dyspnea, and fluid retention, all of which reduce a patient's overall functional ability (70). The significant impact of heart failure on patient morbidity and mortality underscores the importance of understanding and managing this condition.

The protective effects of resveratrol on the heart are attributed to its ability to regulate pathways involved in the development and progression of heart failure (71). One of these pathways is the activation of sirtuins, particularly SIRT1, which helps manage stress response and energy metabolism (72). Resveratrol also demonstrates anti-inflammatory properties by inhibiting NF-κB signaling and reducing oxidative stress (68), both of which play roles in the advancement of heart failure.

There is substantial evidence supporting the role of oxidative stress and subsequent chronic inflammation in the development of heart failure (73,74). Oxidative stress activates several intracellular signaling pathways that control cardiac remodeling, hypertrophy, myocyte survival, apoptosis, and necrosis (75).

In recent decades, the antioxidant and anti-inflammatory properties of resveratrol have been widely studied in numerous rodent models of heart failure. Previous studies have shown that resveratrol can improve both diastolic and systolic heart function, reduce atrial and left ventricular remodeling, and enhance cardiac energetics, all of which contribute to its cardioprotective benefits in heart failure. Over a 10-month period, a study by Ahmet et al. found that resveratrol supplementation (5 mg/kg/day) significantly improved left ventricular systolic performance in a post-infarction heart failure rat model (76). Similarly, another study examined the effects of resveratrol in an isoproterenol-induced post-infarction heart failure rat model. The outcomes of 8 weeks of resveratrol therapy (15 mg/kg/day) demonstrated enhanced systolic left ventricular function, decreased plasma BNP levels, and reduced left ventricular wall thickness and dimensions. Furthermore, resveratrol lowered oxidative stress and improved various intracellular signaling pathways (Akt-1/GSK-3, p38-MAPK, ERK1/2, MKP-1, COX-2, and iNOS uncoupling). Resveratrol showed the potential to sustain left ventricular function and reduce the severity of heart failure within 2 months (77). This implies that a carefully calculated low-dose regimen could be beneficial for preventing the progression of heart failure in patients at risk.

A study by Matsumura et al. used cardiotoxic hydroxyeicosatetraenoic acid (HETE) to induce myocardial infarction and heart failure in a different rat model of post-infarction heart failure in 2018. The results showed that resveratrol therapy (5.82 mg/kg/day) significantly improved ejection fraction and decreased post-infarction left ventricular and atrial remodeling. Surprisingly, the cardioprotective benefits of low-dose resveratrol appeared to be independent of the traditional SIRT1 and antioxidant pathways, indicating a novel mechanism (78). By targeting these pathways, resveratrol

could potentially reduce the risk of heart failure developing or worsening after myocardial infarction.

In a pressure-overload-induced heart failure mouse model, researchers investigated the effects of resveratrol on cardiac anatomy and function. The study results showed that resveratrol (150 mg/kg/day) improved diastolic function, reduced left ventricular diameters and volumes, and decreased heart fibrosis, hypertrophy, and remodeling via antifibrotic and anti-inflammatory actions. Notably, systolic function remained unchanged following 2 weeks of resveratrol supplementation (79). The reduction in inflammatory cytokines like IL-1 and IL-6 observed in clinical studies suggests that resveratrol could help manage chronic inflammation, a significant factor in the progression of heart failure.

Another study revealed that low-dose resveratrol supplementation (2.5 mg/kg/day for 28 days) reversed pressure-overload-induced ventricular hypertrophy and remodeling in rats, accompanied by a substantial decrease in oxidative stress (80).

A recent study by Ma et al. revealed that resveratrol (25 mg/kg/day) decreased myocardial hypertrophy and fibrosis in rats with heart failure by activating SIRT1. Improved mitochondrial activity was achieved through the deacetylation (activation) of PGC-1 and modulation of downstream proteins such as Nrf-1 and Nrf-2 (81). Resveratrol (10 mg/kg/day for 8 weeks) also reduced heart hypertrophy in diabetic rats via SIRT1-mediated antioxidant actions (81).

In many preclinical investigations, resveratrol significantly increased exercise capacity in addition to improving cardiac function and remodeling. Sung et al. demonstrated that resveratrol supplementation (450 mg/kg/day for two weeks) successfully improved fatigue and exercise intolerance in pressure-overload-induced heart failure rats, which was associated with beneficial changes in gut microbiota composition and increased whole-body glucose utilization (82). According to Hart et al., resveratrol supplementation (100 mg/kg/day) for 12 weeks dramatically boosted exercise capacity in rats, mediated by increased mitochondrial biogenesis via the AMPK-SIRT1-PGC-1 pathway activation (83). Preventive use of resveratrol could enhance exercise tolerance, thereby contributing to better overall cardiovascular health.

In a randomized double-blind human clinical study in 2020, researchers produced the first evidence of resveratrol's positive influence on heart failure. This experiment involved 60 outpatients with systolic heart failure in NYHA classes II-III, who were randomly assigned to one of two groups: daily 100 mg resveratrol or a placebo for three months. The resveratrol therapy improved various heart function indices, including systolic and diastolic function, global longitudinal strain, and a significant reduction in cardiac biomarkers linked to heart failure and remodeling (NT-proBNP and galectin-3). Furthermore, exercise tolerance and quality of life increased in the treatment group. Resveratrol also had an anti-inflammatory effect, as evidenced by lower levels of inflammatory cytokines (IL-1 and IL-6). The findings suggested that decreased leukocyte activity might be a key mechanism by which resveratrol exerts its cardioprotective benefits in heart failure. Additionally, patients treated with resveratrol had significantly higher stroke volume, end-diastolic volume, and ejection fraction compared to controls (84). This study highlights resveratrol's potential in improving cardiac function and quality of life in patients with systolic heart failure.

Resveratrol Treatment of Chagas Heart Disease

The leading cause of myocarditis due to infection is Chagas Heart Disease (CHD), caused by the protozoan Trypanosoma cruzi (85). Even after the parasite is eliminated by the immune system, patients can develop cardiomyopathy (85). This cardiomyopathy is often accompanied by cardiac electrical disturbances that can lead to heart failure (85). Although the pathogenesis of CHD is not fully understood, a prominent pathological mechanism for the cardiotoxic effects associated with CHD is oxidative stress (86).

A recent study using mouse models examined the effect of resveratrol on CHD. Compared to control mice, those exposed to resveratrol showed decreased prolonged PR and QTc intervals, elevated heart rates, and corrected sinus arrhythmias (86). Additionally, resveratrol-treated mice showed improved left ventricular ejection fraction, increased stroke volume, and enhanced cardiac output (86). A study by Vilar-Pereira et al. revealed that resveratrol-treated mice exhibited cardioprotective effects through increased AMPK activation compared to control mice (86,87). It was also shown that resveratrol-treated mice had lower levels of Trypanosoma cruzi and reduced ROS compared to control groups (86).

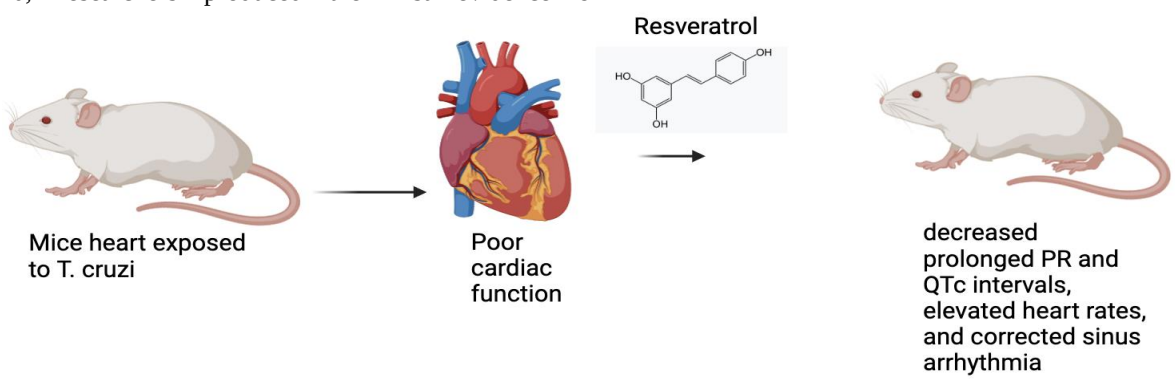

Figure 5 . Resveratrol effect on Mice heart exposed to Trypanosoma Cruzi. Studies from the figure 4 are cited in Table 1. Created with Biorender.com

Resveratrol can act as an antioxidant by upregulating Nrf2, an antioxidant gene, and decreasing the expression of NOX2 and NOX4, which have been implicated in oxidative stress in CHD (88,89,90,91). The reduction of oxidative stress helps prevent the long-term cardiac dysfunctions associated with CHD (92). Research findings also illustrated that resveratrol combined with metformin and tempol has the potential to reverse physiological dysfunctions caused by CHD (86).

Discussion

The comprehensive review of existing literature demonstrates the potential of resveratrol as a therapeutic agent for various cardiovascular conditions, including atherosclerosis, CAD, hypertension, CR, stroke, myocardial ischemia, and heart failure. Its multifaceted properties, such as antioxidant, anti-inflammatory, and vasodilatory effects, contribute to its protective role in cardiovascular health. Furthermore, the safety profile of resveratrol, characterized by mild and transient adverse events, supports its potential use in clinical settings.

Resveratrol's ability to modulate oxidative stress is a recurring theme across the studies reviewed. Oxidative stress is a key player in the pathogenesis of several cardiovascular conditions, leading to endothelial dysfunction, smooth muscle cell proliferation, and chronic inflammation. By neutralizing free radicals, RES mitigates these deleterious effects, thereby reducing the risk and progression of atherosclerosis, CAD, and myocardial ischemia. Furthermore, the compound's anti-inflammatory properties contribute to its protective role in these conditions, as it downregulates pro-inflammatory cytokines and inhibits pathways such as NF-κB that are involved in inflammatory responses.

The review also underscores the significance of RES in managing hypertension. By enhancing nitric oxide (NO) production, RES promotes vasodilation, which is crucial in lowering blood pressure. The compound's ability to inhibit Rac1 and reduce reactive oxygen species (ROS) further underscores its antihypertensive potential. Moreover, studies reviewed show that RES can prevent morphological changes in the cardiovascular system associated with hypertension, such as the atrophy of endothelial cells and smooth muscle cells.

Cardiac remodeling, a pathological process often triggered by myocardial injury, represents another area where RES shows promise. Studies reveal that RES can reduce cardiac fibrosis, inhibit ventricular hypertrophy, and improve overall cardiac function, especially in heart failure models. The activation of sirtuins, particularly SIRT1, appears to be a critical mechanism by which RES exerts these effects, highlighting its role in regulating stress response and energy metabolism in cardiac cells.

Resveratrol's neuroprotective effects in stroke management also merit attention. The compound not only reduces inflammation and oxidative stress in the brain but also promotes neurogenesis and angiogenesis, offering potential therapeutic benefits for ischemic stroke patients. Additionally, RES's ability to extend the therapeutic window of r-tPA, the current standard of care for ischemic stroke, further solidifies its role as a valuable adjunctive treatment in stroke management.

The review also discusses RES's efficacy in treating heart failure, emphasizing its impact on improving cardiac function, reducing oxidative stress, and enhancing exercise tolerance. The positive outcomes observed in both animal models and human clinical trials suggest that RES could be a valuable addition to current heart failure therapies.

Finally, the review touches upon the potential of RES in managing Chagas heart disease (CHD), a less commonly discussed but important cardiovascular condition. The studies reviewed indicate that RES can mitigate the cardiotoxic effects of Trypanosoma cruzi, the causative agent of CHD, by reducing oxidative stress and improving cardiac function.

Conclusion

In conclusion, resveratrol presents as a promising therapeutic agent in the management of a wide range of cardiovascular diseases.

However, it is crucial to note that while preclinical and clinical studies provide promising data, there is a need for further large-scale randomized controlled trials to confirm the efficacy and safety of resveratrol in diverse patient populations. The current research is mainly composed of animal models and in vitro studies. This may not be applicable for humans. Additionally, the issue of bioavailability remains a challenge that requires innovative solutions, such as advanced delivery systems, to maximize the therapeutic potential of resveratrol.

As the burden of cardiovascular diseases continues to grow globally, the exploration of natural compounds like resveratrol offers a valuable avenue for developing accessible and effective treatment options. Future research should focus on optimizing resveratrol's pharmacokinetics, understanding its mechanisms of action, and exploring its long-term effects in various cardiovascular disorders. There should be more research on combining already established treatment with resveratrol and observing if there is an enhancing effect. Long-term research is needed on the side effects of prolonged resveratrol use.

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Abbreviations: Coronary Artery Disease (CAD), Chagas Heart Disease (CHD), cardiac remodeling (CR), heart failure (HF), peripheral arterial disease (PAD), reactive oxygen species (ROS), fibroblast growth factor (FGF), nerve growth factor (NGF), matrix metalloproteinase (MMP),

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