The Sirtuin System: The Holy Grail of Resveratrol?

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Abstract

The oxidative stress theory has been associated with atherosclerosis and has prompted a multitude of studies to evaluate the effects of antioxidants on cardiovascular disease prevention. Resveratrol, a relatively new antioxidant has gained considerable curiosity. This polyphenol stilbene identified in grape skin, is believed to be the main component contributing to the anti-atherosclerotic benefits linked to red wine consumption. It has demonstrated the ability to protect endothelial cells from lipid damage, promote vasodilation via modulation of nitric oxide synthesis, and inhibit platelet aggregation and smooth muscle proliferation. Although the complete mechanism of Resveratrol has yet to be fully elucidated, the Sirtuin system, consisting of 7 highly conserved families of regulator genes, are thought to be instrumental in establishing the various health benefits.

In this article we assess the current applications, mechanism, pharmacokinetics, bioavailability, and safety profile of the novel antioxidant Resveratrol and provide an in-depth review of the influence of the Sirtuin system on the Resveratrol mechanism of action. We resolve that while early data on Resveratrol are promising, the anti-oxidative and ultimately, anti-atherosclerotic potential depends on further clarification of the intricate and complex relationship between Resveratrol and the Sirtruin system.

Keywords

Resveratrol; Reactive oxygen species; Atherosclerosis; Cardiovascular disease

Introduction

Maintaining a healthy diet and lifestyle remains the mainstay of cardiovascular disease risk reduction. The "French Paradox" reflects the reduced incidence of Cardiovascular Disease (CVD) found in some French populations with moderate wine consumption despite a high-fat intake, low exercise, and increased tobacco use [1]. These and other such studies were monumental in developing the current concepts of the widely accepted "Mediterranean Diet". A staple of the diet, red wine contains various cardio protective antioxidants and moderate intake of wine has been linked to reduced cardiovascular eve [2,3].

Progressive research on organic antioxidants found in natural products, such as red wine, have held a central focus in current antioxidant research models. The main ingredient of red wine, the grape, is a well known source of protective phenols and polyphenols that have been associated with CVD risk reduction and prevention against lipoprotein peroxidation.

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Moreover, Resveratrol is a polyphenol compound, has been attributed to various cardiovascular benefits secondary to its antioxidant properties [4–6] (Figure 1). While there appears to be an observational consensus about the cardiovascular benefit of Resveratrol, human clinical trials are still ongoing and premature. Furthermore, pre-clinical human studies have found it difficult to replicate the bioavailability and efficacy of Resveratrol found in early animal models (Table 1).

Resveratrol

The polyphenol stilbene molecule Resveratrol has recently gained much publicity and interest as a novel antioxidant molecule, potentially holding the key towards unlocking the cardio protective factors of red wine. Also known as (3,4',5-trihydroxystilbene), this ancient stilbene has also long been utilized as a component of (Veratrum formosanum) in traditional East Asian medicine [7] and in pre-Colombian medicine in South America (Cassia quinquangulata) [8]. Analysis into recent studies have revealed Resveratrol as a known activator of the protein deacetylase sirtuin 1 (SIRT1) gene, which is thought to mediate anti-proliferative and anti-inflammatory activity due to alteration of gene expression and modulation of numerous metabolic pathways [9–11].

Applications

Resveratrol has demonstrated a wealth of promising benefits, such as anti-aging [12], anti-inflammatory [13], and anti-diabetic [14] effects; and further as a potent anti-viral [15] and anti-neoplastic [16] agent. Additionally, Resveratrol offers great potential as a cardiovascular disease modulating agent, as demonstrated by the abundance of preclinical trials related to heart disease (Table 1).

As a novel agent isolated in the skin of grapes, Resveratrol has demonstrated pronounced cardioprotective potential as it has been shown to enhance coronary relaxation, reduce ventricular arrhythmias, inhibit platelet aggregation and smooth muscle proliferation, improve glucose metabolism, reduce Low-density lipoprotein (LDL) while elevating High-density lipoprotein (HDL) [17]. As such, these cardiovascular effects promote vascular wall integrity and inhibit endothelial dysfunction, thus disrupting the atherosclerotic process (Figure 1).

Mechanism

Despite possessing such promising potential in treating an assortment of human diseases, the exact mechanism by which Resveratrol demonstrates these effects has yet to be fully elucidated as human clinical trials are lacking. Further, despite what seems to be broad and multifactorial applications, Resveratrol is quite a poor direct antioxidant. It was suggested that Resveratrol is less potent then other antioxidants, such as vitamin-C and cysteine [18].

This inadequacy to delineate one encompassing mechanism is likely due to the fact Resveratrol acts as a secondary regulator of a larger more complex biological response system. Recent studies have focused on the Sirtuin system, a complicated regulatory biological response process known to be activated by Resveratrol. This highly conserved family of genes termed silent information regulator genes (SIR) are comprised of seven Sirtuin genes in mammals, SIRT 1 through SIRT 7, and are widely expressed in a variety of tissues. These genes encode for specific (SIRT) NAD+ dependent de-acetylating enzymes and are considered regulatory proteins. Specifically, the subcellular locations of these Sirtuins include the nucleus (SIRT 1,-2,-6,-7), cytoplasm (SIRT-1,-2) and mitochondria (SIRT 3,-4,-5) [19].

SIRT 1 is one of the more extensively studied Sirtuins within the cardiovascular system. In addition to being modulated by Resveratrol, SIRT 1 is highly expressed in the vasculature. It appears to modulate angiogenic activity in periods of vascular remodeling and vascular growth [20,21]. In fact, SIRT-1 has been shown to target endothelial nitric oxide synthase (eNOS) for de-acetylation, thus activating and enhancing endothelial nitric oxide production [22].

The relationship between Resveratrol and SIRT 1 is further apparent via studies which have shown anti-hypertensive effects via modulation of the angiotensin II type I receptor. In vascular smooth muscle, in vivo studies reveal Resveratrol's ability to propagate SIRT1 expression resulted in decreased angiotensin II-induced hypertension [23]. Additionally, SIRT1 has been reported be a regulator of tissue metalloproteinase 3 (TIMP3), an endogenous enzyme which defenses vascular inflammation and is involved in the prevention of atherosclerosis [24].

Furthermore, nuclear SIRT-1 enhanced by Resveratrol was found to induce superoxide dismutase, an antioxidant enzyme which suppressed cell death in cardiomyocytes [25]. These and other studies support the protective effects of Sirtuins on cardiomyocytes via activation of antioxidant encoding genes, thus helping to mitigate the cellular burden of reactive oxygen species [26].

Beyond SIRT-1, SIRT-3 and SIRT-7 also appear to be vital for optimal cardiovascular function. In SIRT-3 deficient mouse models, signs of severe cardiac hypertrophy and interstitial fibrosis were present, when a hypertrophic stimulus was given [27]. Conversely, transgenic mouse models engineered for over-expression of SIRT-3 were significantly less amenable to stimuli-induced hypertrophy [26]. In similar fashion, SIRT-7 deficient mice had myocardium defined by extensive fibrosis and high basal rates of apoptosis, resulting in high levels of cardiomyopathy [28].

Bioavailability

The alcoholic red wine matrix seems to be vital for activity, as primary supplementation with isolated Resveratrol results in low bioavailability [29]. Only when Resveratrol is ingested in the red wine matrix does it posses the bioavailability to achieve the efficacious levels to provide improvement of endothelial dysfunction [30]. Furthermore, studies of Resveratrol in other matrices such as white wine, grape juice, and vegetable juice/homogenate have not yielded promising results [31]. These studies have further underlined the importance of the ripe chemical environment specifically provided by red wine [32].

Metabolism and pharmacokinetics

Studies have postulated the role of detoxifying hepatic enzymes such as, cytochrome p450, as possessing particular importance in the catabolism of Resveratrol [29]. Furthermore, it is quickly metabolized as the active primary Resveratrol molecule possesses a relatively short half life of ~8–14min [33]. Additionally, Quercetine and Ethanol are compounds identified in red wine, which are perhaps necessary to amend the activity of catabolic enzymes, thus augmenting Resveratrol activity [34].

Safety/Adverse effects

Resveratrol has not been identified as toxic or causing adverse effects. However, human clinical trials are lacking at this point. In animal models, up to 300 mg/kg were administered over an extended period without note of adverse effects [35]. Additionally, through in vitro studies Resveratrol has been known to inhibit platelet aggregation [36]. As such, potential

for bleeding may occur with concurrent administration of anticoagulants Heparin or Warfarin, and anti-platelet agents Aspirin or Plavix.

Resveratrol is metabolized by cytochrome P450, and has also been shown to inhibit the activity of the cytochrome [37]. Although not identified in humans, drugs taken concurrently with Resveratrol, which are also metabolized via the hepatic cP450 enzyme, may have increased bioavailability and the potential for subsequent toxicity exists. These drugs include but are not limited to: HMG-CoA reductase inhibitors, calcium channel blockers, and certain anti-arrhythmics, such as Amiodarone.

Conclusions

Resveratrol, a novel molecule found in red wine, and hypothesized to be the key ingredient and possible answer to the "French Paradox", offers great potential benefit as an agent which may amend a multitude of human disorders, chiefly among these, Cardiovascular Disease.

Resveratrol modulates these favorable effects via interaction with Sirtuin molecules, a highly complex regulatory response system which appears sensitive to various metabolic influences. Human clinical research elucidating the relationship between Resveratrol and the Sirtuin system remains vital and necessary. Further investigation is currently ongoing on what appears to be a complex, yet broadly applicable regulatory process.

Acknowledgments

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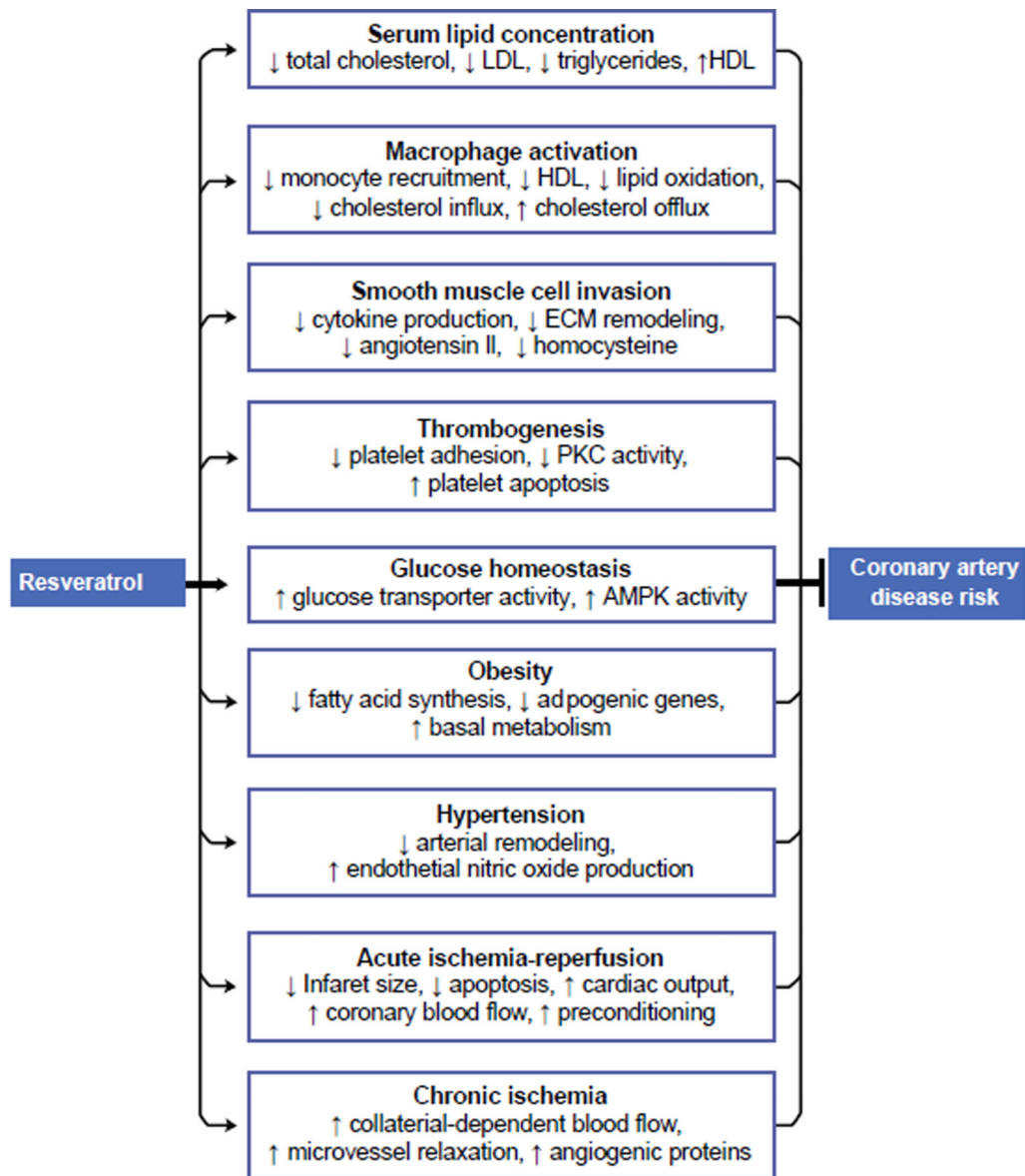
Abbreviations: AMPK: AMP-activated protein kinase; ECM: Extracellular matrix: HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PKC: Protein kinase C

Figure 1.
The many effects of resveratrol on coronary artery disease risk. Resveratrol has been shown to modify a large number of factors that contribute to coronary artery disease. This diagram summarizes the proposed mechanisms by which resveratrol influences these factors and reduces the risk of CAD [51].

Table 1

Pre-Clinical Studies of Resveratrol in Heart Disease.

Study	Investigation Type/Model	Animal Class	Dose	Result
Ischemic Heart Disease +/− Reperfusion Studies				
Sato M et al. [38]	Ischemia/reperfusion	Rat	10 μM	Decreased infarct size
Hung LM et al. [39]	Ischemia/reperfusion by temporary occlusion of Left Main coronary artery	Rat	0.23,2.3,23 μg/kg	Decreased incidence of ventricular fibrillation and tachycardia, decreased LDH, and increased vascular NO
Imamura G et al. [40]	Ischemia/reperfusion	Mouse	10 μM	Decreased infarct size and apoptosis
Bradamante S et al. [41]	Ischemia/reperfusion 24 hrs. after treatment	Rat	1 mg/kg	Functional recovery improvement and increased coronary flow
Das S et al. [42]	Ischemia/reperfusion	Rat	2.5 mg/kg	Functional recovery improvement, decrease in infarct size and apoptosis, induction of VEGF, eNOS, iNOS
Dernek S et al. [43]	Ischemia/reperfusion	Rat	20 μM	Post ischemic recovery improved with chronic treatment, only partial protection with acute dosing
Kaga S et al. [44]	LAD occlusion	Rat	1 mg/kg	Improved ventricular function, decreased infarct size, increased VEGF expression
Coronary Risk Factor Studies				
Wang Z et al. [45]	Hyperlipidemia	Rabbit	3 mg/kg	Decreased thoracic intima layer thickness and plaques, block of dilation by flow mediation
Auger C et al. [46]	Hyperlipidemia	Hamster	0.1428 mg/kg	Decreased Aortic fatty streak accumulation
Fukaw H et al. [47]	Endothelial injury	Mouse	9.6, 96 mg/kg	Decrease in thrombus size and atheroma
Zou JG et al. [48]	Endothelial function	Rabbit	3 mg/kg	Increase in endothelin, decrease of NO blocked
Wang Z et al. [49]	Platelet aggregation	Rabbit	4 mg/kg	Reduced platelet aggregation
Arichi H et al. [50]	Triglyceride synthesis	Mouse	25, 50 mg/kg	Reduced hepatic and adipose lipogenesis