Resveratrol as a Supplemental Therapeutic in Cardiovascular and Metabolic Syndromes: A Critical Review

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Abstract: Metabolic syndrome places patients at high risk to many other health problems, as their bodies are in a perpetual state pro-inflammation and pro-thrombosis. In many cases, a regulated diet and increased exercise is sufficient in rectifying their condition, however for many patients, drug intervention is necessary. In recent years, calorie restriction has been shown to improve the health of patients afflicted with aging-related diseases, specifically those associated with metabolic syndrome, and researchers are now exploring drugs that mimic calorie restriction. Resveratrol mimics a calorie restricted diet as it has been shown to attenuate health benefits, including anti-platelet aggregation, vasorelaxation, atherosclerosis suppression, and lipid metabolism similar to a calorie restricted diet. Additionally, it modulates many of the pathways associated with metabolic syndrome, leading researchers to believe it has potential as a burgeoning therapeutic approach.

Keywords: Resveratrol, metabolic syndrome, calorie restriction, SIRT1.

INTRODUCTION

Metabolic syndrome is a multiplex of medical conditions that predisposes individuals to cardiovascular disease (CVD) [1, 2]. It has been estimated that metabolic syndrome is present in more than 20% of the US adult population [2, 3]. According to the Adult Treatment Panel III, a patient diagnosed with metabolic syndrome displays specific physiological characteristics, including abdominal obesity, atherogenic dyslipidemia (low HDL and high LDL levels), raised blood pressure, insulin insensitivity and is overall in a pro-thrombotic, pro-inflammatory state [4]. Amongst these risk factors, these patients with metabolic syndrome additionally possess life-habit risk factors and emerging risk factors which can potentially further threaten their overall health [4].

Individuals who have metabolic syndrome or who are concerned about developing it can now choose from wide variety of natural, over-the-counter dietary supplements which claim to treat and/or prevent many of the different risk factors associated with the condition. The usefulness of natural dietary supplements in the treatment and prevention of various medical conditions, especially metabolic syndrome, is highly debated, but generally under-researched. The widespread and ever-increasing use of natural supplements, however, has demanded that more basic science research and clinical research be done to address this topic.

Polyphenols are secondary metabolites found in plants that serve as a defense against insects, UV damage, and bacterial and fungal infections. There is good evidence that these substances, when consumed in small amounts, can be useful for treating and reducing chronic diseases, including CVD. Epidemiological studies have indicated that populations who traditionally consume foods rich in certain polyphenols have a lower incidence of chronic inflammatory diseases [5]. The beneficial properties of these compounds are believed to result from their antioxidant and anti-inflammatory capabilities and subsequently, a large number of approved anti-inflammatory drugs are derived from or based on the structure of these compounds [6]. These compounds have the ability to modulate a number of cellular signaling pathways including those involved in anti-platelet aggregation, vasorelaxation, atherosclerosis suppression, and lipid metabolism regulation. This review discusses the cellular pathways affected by metabolic syndrome, and the potential use of polyphenols found in red grape products, particularly resveratrol, for the treatment and prevention of metabolic syndrome.

PATHOBIOLOGY OF METABOLIC SYNDROME

CARDIOVASCULAR DISEASE

The primary clinical outcome of metabolic syndrome is cardiovascular disease [2]. Metabolic syndrome develops and is maintained through a complex interplay of dysfunctions that promote one another [1]. A body afflicted with metabolic syndrome can be generally classified as pro-thrombotic and pro-inflammatory, with defective lipid and glucose metabolism [1, 7]. Understanding the contribution of metabolic risk factors to CVD, including abdominal obesity, hypertriglyceridemia, dislipoproteinemia, hypertension, and hyperglycemia in metabolic syndrome is critical in regard to various drug therapy options [1].

OBESEITY

Obesity has been identified as the main causative factor in the development of metabolic syndrome [8]. In recent years, obesity has become a major worldwide health issue, particularly in developed countries including the United States, where more than half of the American adult...
population can now be considered overweight or obese [9]. The accumulation of abdominal fat is believed to cause local, as well as systemic, oxidative stress [8]. Studies in mice and humans have revealed that the production of reactive oxidative species (ROS), expression of NADPH oxidase, and reduction of antioxidative enzyme levels, occur selectively in adipose tissue [8]. Local oxidative stress is hypothesized to be the driving force behind the dysregulated production and secretion of some adipocytokines (fat derived hormones), including: adiponectin, IL-6, and monocyte chemotactic protein-1 (MCP-1) which promote the pro-thrombotic, pro-inflammatory state of metabolic syndrome [1].

Atherogenic Lipoprotein Phenotype

Lipoprotein particles play an important role in normal physiological function as well as in the pathogenesis of metabolic syndrome. Additionally, dyslipidemia is one of the most prominent risk factors for CAD and metabolic syndrome [10]. Very low-density lipoproteins (VLDLs) are triglyceride-rich particles that are synthesized in the liver and transport triglycerides to adipose tissue and muscle. VLDLs can be hydrolyzed by lipoprotein lipase to become intermediate-density lipoproteins, which, in turn, can be converted to low-density lipoproteins (LDLs) by hepatic lipase. Finally, high-density lipoproteins (HDLs) are responsible for the transport of cholesterol from peripheral tissues back to the liver for degradation and are atheroprotective through this reverse cholesterol transport (RCT) mechanism and has been shown to be antioxidative antithrombotic and anti-inflammatory [10, 11].

The term “atherogenic lipoprotein phenotype” was coined to describe the dyslipidemia that is commonly found in patients with metabolic syndrome. The atherogenic lipoprotein phenotype is characterized by increased plasma triglyceride levels, decreased HDL-cholesterol concentrations and the presence of small, dense LDL particles [12]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines define a normal triglyceride value as <150 mg/dL, and individuals with levels higher than this are considered hypertriglyceridemic [4]. Dietary intake of high fat and high cholesterol foods, and accumulation of visceral fat leads to increased influx of free fatty acids to the liver which stimulates an increase in hepatic triglyceride synthesis and secretion of VLDLs, which raises plasma triglyceride levels [13-15].

Atherosclerosis

The irregular lipid profile, oxidative stress, vascular damage, and proinflammatory state characteristic of the metabolic syndrome all directly contribute to atherosclerosis, the condition that underlies many CVDs. When the vascular endothelium is damaged, an accumulation of intimal lipids, monocytes, and T lymphocytes ensues, which leads to the migration and proliferation of smooth muscle cells in the subintimal layer of the endothelium [16, 17]. In its advanced stages, there is a sequence of plaque growth and ruptures as a result of LDL uptake by macrophages and subsequent release of inflammatory, growth and thrombogenic factors. Plaque formation, along with the chronic inflammation of the cardiovascular endothelium are the hallmarks of atherosclerosis [16, 17].

HDL particles are crucial in atheroprotection as evidenced by their ability to remove cholesterol from these plaques and return it to the liver where is can be eliminated in bile, thereby reversing the progression of atherosclerosis [10]. Additionally, low HDL cholesterol (HDL-C) levels have been long associated with coronary artery disease (CAD) [18]. One of the new features of the ATP III guidelines is the classification of low HDL-C levels as a categorical risk factor and raising the required cut-off level of plasma HDL-C from 35mg/dL to 40 mg/dL as the required level in men [4].

Hyperglycemia

Patients with diabetes are predisposed to accelerated formation of atherosclerosis as the combination of hyperglycemia, excess free fatty acids and insulin resistance contribute to the engendering of adverse metabolic events within the endothelial cell [19]. Further evidence has shown that diabetes-accelerated atherosclerosis is related to hyperglycemia and hyperinsulinemia, which is caused by insulin resistance, as patients with metabolic syndrome usually have a form of Type 1 diabetes, but eventually begin to display reduced insulin production, as in Type 2 diabetes [19]. The transition from Type 1 to Type 2 diabetes may, in part, be the result of protein glycation in pancreatic beta cells, due to chronic hyperglycemia. Ultimately, this glycation can suppress the transcription of the insulin gene further implying glucose toxicity [20].

Oxidative stress dysregulates the secretion of TNF-α and adiponectin, which appear to have antagonistic tendencies in the context of glucose metabolism [21]. The secretion of TNF- α (tumor necrosis factor-α), which promotes insulin resistance via tyrosine kinase activity, is increased, whereas the secretion of adiponectin, which increases insulin sensitivity, is decreased [21, 22]. The altered secretion of both of these adipocytokines serves to further the development of diabetes [21-26].

Oxidative stress has also been shown to promote insulin resistance by impairing insulin-stimulated GLUT4, a facilitative transporter, translocation from an intracellular membrane pool to the plasma membrane which allows glucose to diffuse down its concentration gradient into the cell [27, 28]. ROS are thought to suppress the activation of the insulin stimulated PI 3-kinase signaling cascade that is responsible for releasing GLUT-4 from intracellular storage sites [29]. Additionally, insulin is involved in the stimulation of nitric oxide (NO) production in endothelial tissue. Under normal conditions, the presence of insulin stimulates endothelial tissue to produce NO, leading to vasodilation and increased blood flow to skeletal muscles, where the glucose can be utilized [30]. High levels of ROS are believed to deplete endothelially derived NO. The resulting NO deficiency leads to reduced vasodilatation, which discourages the passage of insulin into target tissues stimulating a negative feedback cycle in which progressive endothelial dysfunction and disturbances in glucose and lipid metabolism develop secondary to the insulin resistance [31].
Hypertension

Elevated blood pressure is strongly associated with obesity and frequently occurs in insulin-resistant patients [2]. A patient is diagnosed with hypertension when their blood pressure is greater than 130/80 mm Hg [19]. Again, systemic oxidative stress is believed to underlie the development of elevated blood pressure as the chronic depletion of endothelially derived NO causes increased constriction in the arteries resulting in hypertension [19]. Endogenous nitric oxide is produced through a group of biotrophiorehemo-flavoproteins called nitric oxide synthases (NOSs) [32]. There are three isoforms of NOSs which are functionally distinguished by their modes of regulation [32]. The two constitutive NOSs, are dormant until calcium/calmodulin (Ca2+/CaM) binding is actuated by transient elevations in intracellular Ca2+. Specifically, endothelial NOS (eNOS) regulate vascular function by controlling NO mediated vasodilation [32]. Therefore, in the absence of intracellular Ca2+, production of NO is decreased and vascular constriction ensues.

Ion channels in endothelial cells are essential in the regulation of Ca2+ signaling [33]. These channels allow for the transport of Ca2+ into vascular smooth muscle cells, promoting functional vasodilation. This pathological tendency towards constriction is maintained through altered voltage-gated “L-type” Ca2+ (CaL) calcium channel expression profiles in vascular smooth muscle cells, specifically, increased expression of CaL channel alpha(1C) subunits [34]. This change is associated with elevated Ca2+ influx and the development of abnormal arterial tone, i.e. “stiffness” [34, 35].

POLYPHENOLS FOR THE TREATMENT OF METABOLIC SYNDROME

Epidemiological studies have shown that diets rich in certain polyphenol containing foods are associated with a reduced risk of CVD. Recent research has begun to elucidate the molecular mechanisms behind the cardioprotective effects of polyphenols [5, 36]. The inverse relationship between polyphenols and cardiovascular disease arose from the occurrence of the “French Paradox,” the low incidence of cardiovascular events despite diets high in saturated fat which was attributed to the regular consumption of red wine [37].

It has been proposed that phenolic flavonoids are capable of exerting free radical–scavenging and metal chelating activity [37]. A reduction in ROS plasma levels can potentially counteract many of the pathological processes that cause metabolic syndrome [37]. It is now apparent, however, in addition to their anti-oxidant capacities, that certain polyphenols can modulate a wide variety cellular pathways associated with both the precipitants of acute cardiovascular events, including the inhibition of platelet aggregation, vasorelaxing activity, modulation of lipid metabolism, and inhibition of low-density lipoprotein oxidation, when unregulated, contribute to CVD [38].

Polyphenols are a group of compounds composed of anthocyanosides (ACs), catechins, proanthocyanidins (PAs), stilbenes, and other phenolic compounds [38]. Plant polyphenols are especially found in grapes and the vast majority of grape-based phenolic research is dedicated to red wines and the cardioprotective properties of grapes have been shown to be located exclusively in the seeds and skins of grapes [39]. PAs (condensed tannins) are high-molecular weight polymers found in grape seeds, skin and stems whereas ACs are water-soluble plant pigments found only in grape skin [38]. Although in one study grape flesh has been shown to possess the same amount of ROS scavenging activity of that of grape skin, however, anthocyanins are only found in the grape skin and account for 50% of the phenolic content of grape skin [39]. These findings explain the abundance of research and information regarding the cardioprotective activity of grape skin, however further studies regarding the phenolic content and cardioprotective implications of grape flesh are needed.

As mentioned earlier, metabolic syndrome is associated with a pro-thrombic and pro-inflammatory state, and when an atherosclerotic plaque ruptures, platelets aggregate and form clots. Clot formation is the major proximate cause of many dangerous cardiovascular events. Some polyphenols have been shown to have an inhibitory effect on platelet aggregation in vivo in both animals and humans [40]. This anti-platelet aggregation is attributed to the phenols ability to reduce LDL oxidation, increase HDL-C levels and by interfering with platelet aggregation and function [5, 40-43].

Additionally, the fact that regular alcohol consumption can decrease the risk of life threatening cardiovascular events has been well documented [44-49]. Furthermore, epidemiological studies revealed that these favorable clinical outcomes were correlated with red wine consumption rather than beer or spirits [5, 36, 44, 50]. In studies where alcohol was used as an anti-platelet aggregation agent, it was found that subjects who consumed ethanol alone experienced an increase in platelet reactivity upon alcohol withdrawal, referred to as the “rebound effect.” This reactivity however, was not seen in moderate red wine drinkers and this protective effect was associated with red wine polyphenols [40].

This belief that polyphenols are the main component of red wine responsible for its cardioprotective effects has been bolstered by studies that have shown that red wine offers superior benefits in comparison to white wines [43]. Additionally, purple grape juice, which contains many of the same polyphenols as red wine has similar cardioprotective effects further implicating the inverse relationship between polyphenols and cardiovascular events in grape skin versus grape flesh [43, 51-54].

There has been extensive research done on the topic of cardiovascular health and red grape products/red grape polyphenols, however, it is important to identify exactly what subjects are administered in each study. It is still not understood exactly if it is the phenol itself, or a combination of phenols and their metabolites that reduce the incidence of CVD [40]. If a red grape product is received by subjects in a study, beneficial effects cannot be attributed to particular polyphenolic components that are present in that product. Conversely, if a specific polyphenolic compound is used in a study, one cannot make decisive conclusions regarding the benefits of red grape products, because the compound in question may not be available or present in the necessary
concentrations to confer the benefits? It is this heterogeneity of experimental conditions that could explain the various physiological outcomes obtained in addition to the multitude of various cellular processes that polyphenols effect [40].

POLYPHENOL EFFECTS ON CELLULAR AND BIOCHEMICAL PROCESSES

Polyphenols affect numerous cellular and biochemical processes, especially those involved in aging, tumorogenesis, and cardiovascular health. Of particular importance here are the mechanisms by which polyphenols are cardioprotective, especially with regard to inflammation, platelet aggregation, lipid metabolism and LDL oxidation, all of which are associated with metabolic syndrome [38, 40].

The reduction of inflammation is an important target in the treatment of metabolic syndrome. With regard to inflammatory mechanisms, polyphenols have been shown to inhibit pro-inflammatory enzymes including cyclooxygenase (COX-2), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS) via activation of peroxisome proliferators-activated receptor gamma (PPAR γ). Also, phenolic compounds have been shown to inhibit phosphoinositide 3-kinases (PI 3-kinase), tyrosine kinases, nuclear factor-kappa B (NF-κB), the expression endothelin-1 (ET-1), and the activation of sirtuin-1 (SIRT1) [38, 55, 56].

A number of other mediators of inflammation are believed to be inhibited by some polyphenols, including the COX and LOX pathways which are responsible for metabolizing arachidonic acid into prostaglandins and leukotrienes, respectively [57-59]. COX-1 is constitutively expressed in most cells, where COX-2 is mostly shows elevated expression in macrophages and mast cells upon stimulation from pro-inflammatory cytokines including interleukine-1 (IL-1) and interleukine-6 (IL-6) [56].

Commonly administered non-steroidal anti-inflammatory drugs (NSAIDs) have provided irreversible inhibition of COX-1 and COX-2 and subsequent formation of prostaglandins, however, there are numerous side effects and drug interactions associated with NSAIDs, which has lead to the study of phenolic compounds as a substitute for NSAIDs [56, 60, 61]. Certain polyphenols have inhibited the production of arachidonic acid, prostaglandins and leukotrienes associated with COX-2 most likely through the suppression of NF-κB [56].

NF-κB is a critical transcription factor that is an upstream inflammatory mediator that regulates over 200 genes involved in inflammatory response; it is an increase in the NF-κB activation that leads to the pro-inflammatory state characteristic of patients with metabolic syndrome [62]. NF-κB is a transcription factor for both vascular cell adhesion molecule-1 (VCAM-1) and endothelial-leukocyte adhesion molecule-1 (ELAM-1), which are responsible for monocyte adhesion to endothelium, an essential step in the development of atherogenic plaques [62, 63].

NF-κB activation also increases the expression of interleukine-1 (IL-1) and interleukine-6 (IL-6), two key inflammatory cytokines that can activate COX-2 expression in pro-inflammatory cells [64, 65]. Inflammation has been shown to promote endothelial dysfunction, reduce the availability of endothelially derived NO, and increase oxidative stress [66]. Several polyphenols have been shown to have an inhibitory effect on NF-κB activation by interfering with its subunits and preventing NF-κB translocation to the nucleus thereby inhibiting NF-κB induced expression of other pro-inflammatory genes [56].

Additionally, iNOS is involved in the inflammatory response and is up regulated upon stimulation by inflammation inducing agents and in the presence of cytokines [67]. Because iNOS is Ca²⁺-independent, NO production from iNOS is sustained at a high level. In endothelial cells, pro-inflammatory agents induce the production of NO by iNOS expression but reduce it by inhibiting eNOS expression [32, 68]. Some polyphenols have been shown to reduce the effects of iNOS, which can have positive effects on endothelial function and glucose metabolism through the reduction of systemic inflammation and regulate normal eNOS function [68]. Other polyphenols have been shown to stimulate eNOS and regulated NO production, which can help to reduce blood pressure, as well as promote endothelial function. Some polyphenols have shown inhibition of LPS-stimulated NO production and iNOS gene expression and also enhance endothelium-dependent vascular relaxation through an increase in NO production via eNOS [68].

Sirtuin-1 (SIRT1) is a NAD⁺-dependent histone deacetylase that may regulate senescence, metabolism, and apoptosis [55, 62]. SIRT1 has the ability to inhibit the transactivation of NF-κB by binding to its RelA/p65 subunit [55, 62]. Activation of SIRT1 has also been shown to improve insulin sensitivity under insulin-resistant conditions in vivo [69]. There is also evidence that SIRT1 reduces the formation, proliferation, and differentiation of adipocytes [70, 71]. In a 2007 study, Kuningas et al. identified a single nucleotide polymorphism in the SIRT1 gene associated with low cardiovascular mortality. This finding strongly suggests that the normal cellular activities of SIRT1 in humans are important for cardiovascular health and, perhaps, the prevention of metabolic syndrome [72]. Resveratrol, a polyphenol found in red grapes has been shown to activate SIRT1, and subsequently improve insulin sensitivity, lower plasma glucose, and increase mitochondrial capacity in obese mice [55].

Endothelin-1 (ET-1) is a small peptide produced by the vascular endothelium that acts as a vasoconstrictor upon activation from insulin [73, 74]. Elevated levels of ET-1 are associated with metabolic syndrome, specifically as a result of hyperinsulinemia [73]. In these patients, as vasodilator function decreases, vasoconstriction increases as a result of increased synthesis of ET-1 which is a direct result of prothrombotic, pro-inflammatory vascular changes as a result of metabolic syndrome [75]. Endothelial cell function can be regulated through simulation of mechanical forces that modulate vascular homeostasis mechanisms [76]. Laminar shear stress is the frictional force that is caused by blood flow over the endothelium, an important regulatory factor which induces vasodilation by increasing levels of endothelial NO and inhibits vasoconstriction by suppressing ET-1 production [75, 76]. It is believed that certain polyphenols can improve endothelial dysfunction and hypertension by reducing the expression of ET-1 [75]. It has
been theorized that some polyphenolic compounds can create a “pseudo-laminar shear stress response” and may play a critical role in the regulation of essential hypertension, hyperglycemia, atherosclerosis, and hypercholesterolemia [75].

RESVERATROL

Out of all of the polyphenols found in red grape products, resveratrol is perhaps the best studied. Not only does it hold therapeutic promise for atherogenic disorders it has received much attention for its potential in the prevention and treatment cancer, viral infection, neurodegeneration, and inflammation [77]. The majority of these studies, however, have focused on the in vitro evidence and animal studies. There is little information regarding the health benefits of resveratrol in humans, including dosing, dose-response relationships, and side effects of the drug. Subsequently, these studies will be discussed below without regard to human effects of resveratrol.

Antioxidant Capacities

Initially, it was thought that one of the ways in which resveratrol promoted cardiovascular health was through its own antioxidant capacities. However, despite the promising in vitro studies, resveratrol proved to be a poor scavenger of ROS in vivo. It is now thought that resveratrol has the ability to increase oxidative stress resistance through the induction other endogenous ROS scavengers, such as mitochondrial superoxide dismutase (MnSOD) which when overexpressed elicits a reduction in intracellular oxidative stress [77]. This reduction in oxidative stress leads to less apoptotic death as a result of decreased mitochondrial dysfunction in various diseases [77].

Additionally, Csiszar et al. conducted study that analyzed the effect of resveratrol on cigarette smoke-induced vascular oxidative stress and inflammation by activation of SIR2/SIRT1 (2008). These findings substantiated previous studies regarding resveratrol’s ability to induce ROS scavengers including SIR2/SIRT1 as the down-regulation of SIRT1 prevented antioxidant capacity of resveratrol while pretreatment with resveratrol decreased CSE-induced ROS production [78]. Also, it was shown that H2O2 plasma levels were significantly reduced by resveratrol treatment as it reduces LDL peroxidation, which corroborates with Robb, 2007’s findings that resveratrol induces MsSOD activity and therefore increases ROS scavenging [78, 79].

Anti-Inflammatory

Resveratrol can inhibit the activation of the pro-inflammatory transcription factor, NF-κB, resulting in reduced expression of inflammatory mediators, such as iNOS and COX, in cultured macrophages [80-82]. Additionally, in SIRT1 knockdown experiments, the inhibitory effect of resveratrol NF-κB activity was reduced in vitro and in vivo [78]. The assumption that SIRT1 controls NF-κB activation via physical interaction and deacetylation of RelA/p65 subunit is supported by the finding that overexpression of SIRT1 inhibits NF-κB activation mediated by its anti-oxidant action [78]. Additionally, it was shown that cigarette smoke extract (CSE) induced up-regulation of ICAM-1, iNOS, IL-6, and TNF- α inflammatory markers which are known to be modulated by NF-κB [78].

Anti-Thrombotic

It has been proposed that resveratrol has anti-platelet mechanism of action. Shen et al. suggest that resveratrol may be able to achieve this through the inhibition the p38 MAPK-cytosolic phospholipase A(2)-arachidonic acid-TxA2-[Ca2+]i cascade and the activation of NO/cyclic GMP, resulting in inhibition of phospholipase C and/or PKC activation in platelets [83]. Also, it is possible that resveratrol could preferentially inhibit COX1, which produces thromboxane A2 (TxA2), a vasoconstrictor and platelet aggregator, over COX2, which produces prostacyclin, anti-platelet aggregator and a vasodilator [79]. The inhibition of TxA2 promotes blood flow and reduces blood clotting, creating an anti-thrombus environment [79]. In addition, under certain conditions, resveratrol induced inactivation of COX1 is irreversible, suggesting that even transient exposures to resveratrol can have long-term implications for cardioprotection [79].

Hyperglycemia

Resveratrol is also a potent SIRT1 activator [71, 78, 79, 84, 85]. Through the activation of SIRT1 it is believed that resveratrol can modulate energy homeostasis in addition to its anti-inflammatory activity. In mice, treatment with resveratrol was found to protect against diet-induced obesity and insulin resistance [84]. These mice demonstrated increased aerobic capacity and induction of genes associated with oxidative phosphorylation and mitochondrial biogenesis [84]. These outcomes can be attributed an increase in peroxisome proliferator-activated receptor-γ coactivator 1α (PCG-1α) activity, a result of decreased PCG-1α acetylation via resveratrol induced SIRT1 activation [79, 84, 85].

CONCLUSION

One of the main causes of atherosclerotic CVD is metabolic syndrome, a multiplex of medical conditions that generally classifies patients as pro-thrombotic and pro-inflammatory, with a defective lipid and glucose metabolism [1, 2, 7]. After years of research and clinical trials, traditional therapeutic approaches are not as effective as a calorie-restricted diet and regular exercise in preventing and treating aging-related diseases [79, 84].

For many patients with metabolic syndrome, lifestyle changes including increased exercise, weight reduction, and an anti-atherogenic diet is sufficient as a treatment option. However, patients with advanced stages of metabolic syndrome require drug therapy, which is most likely to include polypharmacy which increases costs and reduces compliance for patients [79]. It is based on this knowledge that research has focused on exploring the mechanisms by which the conditions of metabolic syndrome are physiologically regulated in order to reduce the incidence of CVD.

It has been shown in epidemiological studies that populations who traditionally consume foods rich in certain polyphenols have a lower incidence of chronic inflammatory diseases [5, 36]. These studies triggered the effort to explore these compounds as an effective treatment for metabolic syndrome and subsequent CVD. Although studies using
wine and grape extracts containing various anthocyanosides (ACs) and proanthocyanidins (PAs) have shown vasoprotective activities, the discovery of resveratrol has provoked a new approach to incorporating polyphenols in cardiovascular research [79]. Resveratrol has been a compound of interest in numerous studies; however, it is unclear to what extent benefits of red grape products can be attributed to resveratrol alone. Additionally, due to insufficient research it is not easy to make direct comparisons between the beneficial effects of a mixture of polyphenols such as those found in red grape products and pure resveratrol.

Although the research on resveratrol has been extensive, the exact mechanism by which resveratrol has a wide range of beneficial effects including anti-platelet aggregation, vasorelaxation, atherosclerosis suppression, and lipid metabolism regulation is not exactly known [79]. It has however, been shown that resveratrol mimics calorie restriction in vivo and as an unregulated glucose metabolism is a key factor in metabolic syndrome; resveratrol is an attractive approach to current cardiovascular health [79, 84].

It has been known that calorie restriction has the ability to modulate metabolism in a way that can increase insulin sensitivity and positively affect glucose homeostasis. Research has thus been directed to evaluate drug therapies that would mimic a calorie restricted diet, as it is unlikely that all patients with metabolic syndrome are willing and able to maintain a regulated diet and exercise schedule. It has been shown by Baur, et al. 2006, that resveratrol given to middle-aged mice on a high-calorie diet significantly increased their survival similar to that of mice on a standard diet [84]. In addition, the resveratrol-treated mice exhibited greater insulin sensitivity as evidenced by a decreased level of markers that predict the onset of diabetes versus that of the mice only on a high-calorie [84]. Also, resveratrol treated mice exhibited greater mitochondrial number and overall improved motor function in addition to increased AMP-activated protein kinase (AMPK) and peroxisome proliferators-activated receptor-γ coactivator 1α (PGC-1α) levels [84]. It has been proposed that these effects are a result of resveratrol primarily working through SIRT1, a principal modulator of pathways downstream from of calorie restriction [55].

According to Milne, 2007, resveratrol activates SIRT1 as a mimetic of calorie restriction, and induced anti-aging effects [55]. However, from pharmokinetic studies, resveratrol is rapidly metabolized in vivo [79]. These results have led some researchers to explore other avenues that SIRT1 can be induced and have focused on identifying a number small molecule activators that are structurally different and vastly more potent that resveratrol. Thus far these small molecules have been investigated in vivo mice models including diet induced and genetically obese mice. In both of these models, improved insulin sensitivity, lower plasma glucose, and increased mitochondrial capacity were noted [55].

Finally, in a recent study, low doses of resveratrol were found to partially mimic calorie restriction and retard aging parameters in vivo [86]. Through feeding mice a control diet and supplementing a low dosage of resveratrol (4.9 m kg⁻¹ day⁻¹), gene expression profiles of aging was noted [86]. It was shown that a level of resveratrol that is easily obtained through dietary supplementation is as effective in opposing the majority of cardiac, age-related gene expression compared to calorie restriction alone [86]. These age-related gene expression profiles were analyzed by comparing transcriptional profiles of young and old mice. There were 1,029 genes that changed with respect to ageing in the heart, and overall 947 genes were opposed by resveratrol as compared to 921 with calorie restriction. Additionally, in other tissues, similar effects between calorie restriction and the control diet supplemented with resveratrol anti-aging gene expression was noted [86].

Ultimately, it was shown that resveratrol in doses that is readily achieved in humans, administered to mice, mimics similar beneficial effects produced by a calorie restricted diet, including an increase in glucose uptake (approximately 25 mg/dL, as compared to the young control), cardiac function as seen in a reduction in isovolumetric relaxation time and myocardial performance versus the old control [86], aging related gene expression as noted above, and is a potential therapeutic approach for treating metabolic syndrome [86].

Although several studies have indicated that resveratrol can activate SIRT1 and subsequent downstream pathways that have an effect on processes that underlie metabolic syndrome; serious doubts had been raised regarding the feasibility of achieving sufficient levels of resveratrol to definitively justify it as a burgeoning therapeutic approach. Upon the recent publication regarding low doses of resveratrol acting as a calorie restriction mimetic in anti-aging gene expression profiles, it seems that more studies regarding resveratrol at these concentrations need to be conducted. Also, as SIRT1 activation modulates pathways downstream of calorie restriction, it appears that other small activators of SIRT1 need to be further investigated to identify endogenous regulators of SIRT1. Overall, the ways in which resveratrol affects the pathways that are dysregulated in metabolic syndrome are overwhelming, and further research needs to be conducted in order to fully realize the potential of resveratrol as a therapeutic approach in aging related diseases, including metabolic syndrome.

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Resveratrol and Metabolic Syndrome


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