



## AGEs INHIBITION & SIRTUIN ACTIVATION TO PREVENT, PROTECT & REPAIR **CARDIAC INFLAMMATION**

- REDUCING CHRONIC INFLAMMATION
- IMPROVING MYOCARDIAL SUBSTRATE UTILIZATION



# Aisa

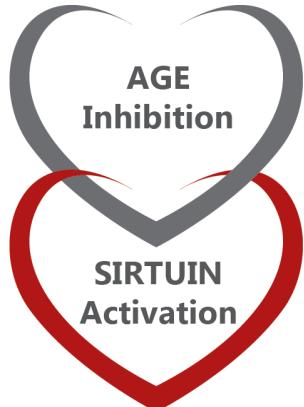
Benfotiamine 50 mg, Pyridoxamine Dihydrochloride 25 mg,  
Levocarnitine 50 mg & Resveratrol 25 mg Tablets

A Multistage **Anti Inflammatory Antioxidant**  
that **Improves Mitochondrial Biogenesis**

**Oxidative Stress (ROS & RNS) accelerates inflammation  
and apoptosis, which in turn causes Cardiomyocyte  
Hypertrophy, Fibroblast proliferation, resulting  
in Cardiac Remodeling (Fibrosis)<sup>1</sup>**



**Prevents Progression from Hypertension to Cardiac Failure<sup>8,15</sup>**



#### **Protects Tissues & Organs**

Prevents accumulation of AGEs & Cellular Debris<sup>2</sup>  
Prevents triggering of Inflammatory Cytokines & TGFβ<sup>3</sup>  
Prevents Mitochondrial Dysfunction<sup>4</sup>

#### **Repairs Tissues & Organs**

Inhibits Inflammatory Cytokines & TGFβ<sup>5</sup>  
Improves Mitochondrial Function & Biogenesis<sup>6</sup>  
Activates Nrf2 & Endogenous Antioxidant Systems<sup>7</sup>

# Aisa

**Prevents... Protects... & Repairs...**  
*Beyond plain Antioxidants*

**cidis**  
**apex**

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# Resveratrol: A promising adjuvant for enhanced cardioprotection

## CARDIOVASCULAR DISEASES: BURDEN WORLDWIDE AND IN INDIA

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality globally. They account for almost 31% of all global deaths.<sup>1</sup> The high CVD burden in the developing countries may be due to an escalating incidence of atherosclerotic diseases, high presence of risk factors such as diabetes, obesity, dyslipidemia and hypertension, development of the risk factors at an early age, and significant size of population.<sup>2</sup> In India as well, CVDs have acquired the status of being the leading cause of mortality, with majority of deaths being related to ischemic heart disease and stroke.<sup>3</sup> Therefore, it is necessary to curtail the burden by closely monitoring different disease aspects and implying interventional policies with the aim to prevent, control and treat CVDs and the associated risk factors.<sup>4</sup>

Diabetes is a common comorbidity and risk factor for CVDs. It is a public health menace, frequently associated with development of coronary heart disease, peripheral arterial disease, stroke, cardiomyopathy and congestive heart failure.<sup>5</sup> Vascular complications of diabetes are associated with two-four-fold increase in the occurrence of coronary artery disease and stroke, and two-eight-fold increase in the risk of heart failure. The pronounced development of CVDs in diabetes may be linked with composite interplay of traditional and non-traditional risk factors (Table 1). The risk factors can present as common factor in diabetes and cardiovascular disease suggesting possible independent association and supporting the hypothesis of common origin.<sup>6</sup>

## DIETARY ADVANCED GLYCATION END PRODUCTS

A diverse group of agents with high oxidative potential have pathogenic role in diabetes, cardiovascular complications and in several other chronic diseases.<sup>7,8</sup> Advanced glycation end products (AGEs) and other species with oxidative potential are

**Table 1: Risk factors predisposing to development of cardiovascular diseases in diabetes**

Conventional	Non-conventional
<ul style="list-style-type: none"><li>Dyslipidemia</li><li>Obesity</li><li>Hypertension</li><li>Abdominal obesity</li><li>Lack of physical exercise</li><li>Cigarette smoking</li></ul>	<ul style="list-style-type: none"><li>Insulin resistance and hyperinsulinemia</li><li>Glucose variability</li><li>Postprandial glycemic excursions</li><li>Hematological factors</li><li>Thrombogenic factors</li><li>Microalbuminuria</li><li>Inflammation C-reactive protein</li><li>Homocysteine and vitamins</li><li>Erectile dysfunction</li><li>Genetics and epigenetics</li></ul>

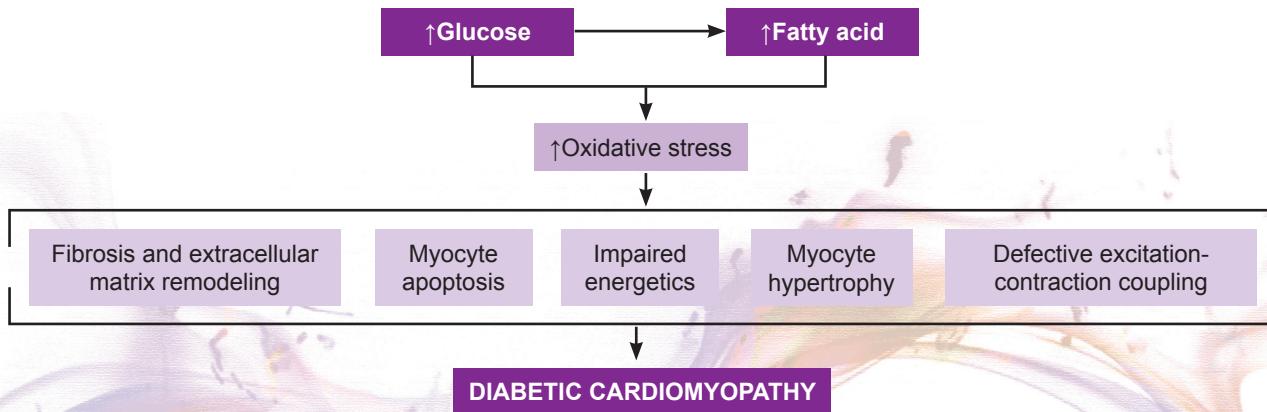
**Adapted from:** Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World Journal of Diabetes.* 2014;5(4): 444-470.

generated through “Maillard or browning reaction” which is a nonenzymatic reaction between sugars and free amino groups of proteins, lipids and nucleic acids. Although, AGE generation is normal part of metabolic process but its excessive generation and accumulation in tissues and circulation is pathogenic. AGEs are capable of promoting oxidative stress and inflammation mediated by two ways; firstly by binding with cell surface receptors and secondly by altering the structure and function of body proteins.<sup>8</sup>

AGEs are not only formed endogenously during metabolic processes, but are also derived from exogenous sources. Heat processed modern diet is a significant source of AGEs. Dietary AGEs are intricately involved in causing inflammation and oxidative stress, and are linked with recent epidemic of CVDs and diabetes. Therapeutic diets have also drawn considerable attention in recent times; these diets are rich in proteins and



**Figure 1** Changes in metabolism, increased oxidative stress and their relevance to diabetic cardiomyopathy



Adapted from: 1. Amaral N, Okonko DO. Metabolic abnormalities of the heart in type II diabetes. *Diabetes & Vascular Disease Research*. 2015, Vol. 12(4) 239– 248. 2. Sung MM, Hamza SM, Dyck JR. Myocardial metabolism in diabetic cardiomyopathy: potential therapeutic targets. *Antioxid Redox Signal*. 2015 Jun 10;22(17):1606-30.

fats and low in carbohydrates and may exaggerate dietary AGE production and contribute to oxidative milieu.<sup>8,9</sup> Likewise, reactive carbonyl species may also have exogenous and endogenous source. The main sources being industrial pollutants, cigarette smoke, food additives and browned food. It is thus important to understand the role of exogenous sources such as diet in generation of reactive species, and introduce modifications guiding reduction in generation of these agents.<sup>7,8,10</sup>

### BIOLOGICAL MECHANISMS CONTRIBUTING TO CVDs

Cardiovascular diseases thrive in the background of obesity, insulin resistance and type 2 diabetes. The pathogenic development of CVDs in diabetes is believed to be an intricate interplay of several mechanisms which remain to be fully explored; foremost being defects in myocardial energy metabolism and calcium signaling. On the backdrop, increase in lipid peroxidation, accumulation of intramyocardial triglyceride and aberration in glucose utilization - attributable to metabolic disturbances - significantly contribute towards diabetic cardiomyopathy changes. The collection of problems leads to exaggerated oxidative stress, mitochondrial dysfunction and apoptosis of cardiac cells.<sup>11</sup>

Figure 1 depicts the possible mechanisms involved in development of diabetes related cardiomyopathy. Hyperglycemia and AGEs have putative role in complicating diabetic cardiomyopathy. AGEs augment the production of reactive oxygen species which are implied in destroying

collagen leading to cardiac fibrosis and stiffness, damaging SERCA resulting in diastolic impairment and the ryanodine receptor contributing to contractile impairment, myocardial hypertrophy, and cardiac insufficiency.<sup>12,13</sup>

Oxidative stress in synchronization with loss of metabolic homeostasis, chronic low grade inflammation and aberrant Transforming growth factor-beta (TGF-beta) signaling worsen the cardiovascular health of an individual.<sup>14</sup> Up-regulation of myocardial TGF-beta expression has been shown in myocardial infarction and cardiac hypertrophy, and in patients with dilated or hypertrophic cardiomyopathy.<sup>15,16</sup>

Although in early stages, TGF-beta is implied in repair of lesion. It is considered that in later and advanced stages of atherosclerotic lesions, selective defects in TGF-beta signaling can disrupt otherwise coordinated pathways of tissue regeneration. In this context, TGF-beta is believed to be an important contributor to arterial calcification as well.<sup>17</sup> TGF-beta has been elucidated to advance the ROS formation by induction of NOX-4 expression. The worsening effect of NOX-4 may be attributed to the transcription factor NRF2 mediated loss of antioxidant defense. In fact, the NRF2 protective mechanisms become less efficient with aging, which is presumed to accelerate disease progression.<sup>14</sup>

### Pathogenic role of chronic low grade inflammation in CVDs

Chronic low grade inflammation complicates the course of several cardiovascular diseases.<sup>11</sup> Circulating levels of acute-phase proteins such as C-reactive proteins (CRP) are related



with and predict the onset of CVDs, in pre-existing diseased condition or healthy state. High levels of interleukin 6 and CRP have been associated with augmented risk of all cause mortality in the elderly.<sup>18</sup>

Inflammatory pathways are pathologically linked with the development of atherosclerosis and information on potential linkages between dyslipidemia and inflammation is increasing continuously. Majority of evidences suggest linear association, dyslipidemia leading to atherogenesis. However, inflammation mediated aberration in lipid metabolism can arise vicious process of inflammation-dyslipidemia-inflammation as well as promote the formation of atherosclerotic plaque inside coronary vessels.<sup>19</sup> Inflammatory markers pace up the development of hypertension in normotensives and worsen hypertensive state in affected individuals. Fluctuation in inflammatory markers may foresee target organ damage and future cardiovascular events in patients with hypertension.<sup>20</sup>

Likewise, in chronic heart failure, inflammatory markers have direct effect on cardiac myocytes, fibroblasts and  $\beta$ -adrenergic receptors translating to hypertrophy, fibrosis and impaired cardiac contractility, respectively, or induce apoptosis.<sup>21</sup> Tumour necrosis factor-alpha (TNF- $\alpha$ ), a proinflammatory cytokine, contributes to progression of disease by causing apoptosis and necrosis of myocytes. Fas (Apo-1) of TNF family, has been shown to increase in heart failure. Inhibition of this marker is associated with decrease in post infarct ventricular remodeling and improves survival.<sup>22</sup>

Augmented production of superoxides activate few major pathways that in concert to cause defects in angiogenesis, activate proinflammatory pathways and commence lasting epigenetic state that translates to endothelial dysfunction. Further, superoxides also deactivate anti-atherosclerotic enzymes such as endothelial nitric oxide synthase and prostacyclin synthase.<sup>23,24</sup> Among AGEs, carboxymethyllysine, methylglyoxal -derivatives, and others AGEs have been identified as potent inducers of inflammation.<sup>25</sup>

### **NEED FOR PREVENTIVE AND ADJUVANT THERAPY FOR ENHANCED CARDIOPROTECTION: FOCUS ON RESVERATROL**

It is evident that there is a profound association between CVDs and deranged metabolic milieu. Diabetes management relies on control of hyperglycemia; however, due to its cardiovascular consequences, it is necessary to account for optimal cardioprotection in addition. Thus, management should be comprehensive entailing glycemic control and cardioprotection, in addition to control of dietary AGEs and AGE inhibition.<sup>7,8,10,26</sup>

It is well-recognized that the treatment in most patients will require non-pharmacological and pharmacological interventions. Recent stress has been laid on search of appropriate adjuvant therapy that is easily available, targets multiple underlying pathomechanisms, and has pleiotropic benefits. As a result, antioxidant therapies such as polyphenols are now being considered as potential coadjuvants.<sup>27</sup>

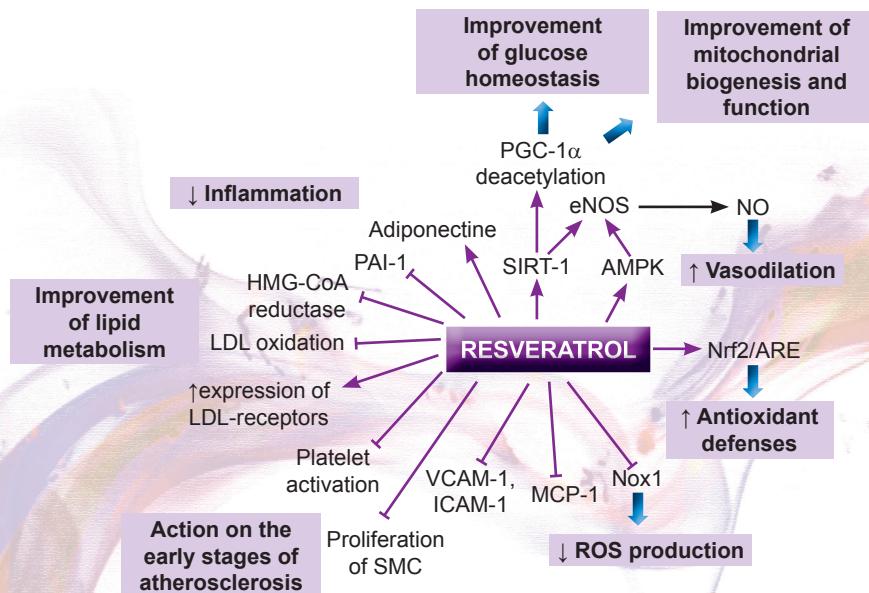
In this regards, cardioprotective benefits of polyphenolic compounds such as resveratrol are gaining popularity. Resveratrol, which is abundant in the seeds and skins of grapes, red wine, mulberries, peanuts, and rhubarb, exerts multitudinous health benefits. It has a key role in activating intracellular pathways akin to those activated by calorie restriction. Pouring evidences have highlighted constellation of properties possessed by resveratrol; antioxidant, antiapoptotic, antihypercholesterolemic, antidiabetic, and angiogenic being few of them.<sup>28</sup>

In particular, sirtuin-1 (SIRT-1) activation mediated via resveratrol has been appreciated remarkably. The sirtuin class of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases is believed to be one of the key targets of resveratrol. Among the several sirtuins currently identified, SIRT-1 mediates longevity. Further, sirtuins govern metabolic control (gluconeogenesis and glycolysis in liver, lipid metabolism), gene repression, cell survival and apoptosis, DNA repair, inflammatory processes, neuroprotection and aging.<sup>29</sup> In essence, sirtuins may improve survival by alleviating oxidative stress in cells during adversity. SIRT-1 has been implied in improving mitochondrial function. A study assessed sirtuin expression and regulation in response to resveratrol administration in cardiovascular complication of diabetes. The myocardial changes subsequent to resveratrol administration were analyzed in experimental models induced with type 1 diabetes or type 2 diabetes. It was elucidated that sirtuin expression which is generally disturbed in cardiovascular complications of diabetes was normalized by administration of resveratrol.<sup>30</sup>

The resveratrol mediated cardioprotection is significant and believed to be analogous to 25% calorie restriction over 6 years. Studies have shown that modulations of different strategic mechanisms impart potential cardiovascular benefits to resveratrol (Figure 2) these include decrease in platelet aggregation, blood vessel dilatation, anti-atherosclerotic, reduction in lipid peroxidation, reduction in endothelin-1, anti-apoptotic, anti-hypertensive, reduction in oxidative stress and improvement in serum cholesterol and triglyceride concentrations.<sup>31,32</sup> The proangiogenic properties of resveratrol



**Figure 2** Potential cardioprotective properties of resveratrol



**Abbreviations:** Nox1: NADPH oxidase 1; MCP-1: monocyte chemotactic protein-1; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; SMC: smooth muscle cells; LDL: low density lipoprotein; HMG-CoA reductase: 3-hydroxy-3-methyl-glutaryl-CoA reductase; PAI-1: plasminogen activator inhibitor-1; Nrf2: nuclear factor (erythroid-derived 2)-like 2; ARE: antioxidant response element; PGC-1α: peroxisome proliferator-activated receptor-γ co-activator 1α; SIRT-1: silent regulator 1; eNOS: endothelial NO synthase; AMPK: activated protein kinase; ROS: reactive oxygen species

**Source:** Dominique Bonnefont-Rousselot. Resveratrol and Cardiovascular Diseases. Nutrients 2016, 8, 250. Available at: <http://www.mdpi.com/2072-6643/8/5/250>. Accessed on: 7.11.2016.

seem to be due to its capability to activate phosphoinositide-3 kinase/Akt and the mitogen-activated protein kinases/extracellular-regulated kinase-mediated signaling pathways. These pathways help in **upregulation of cellular protective molecules such as endothelial nitric oxide synthase (eNOS)** which increase vascular protective nitric oxide (NO), and **vascular endothelial growth factor (VEGF)** and **matrix metalloproteinases** that induce NO-dependent angiogenesis. Furthermore, **mitochondrial biogenesis in response to resveratrol administration protects endothelium from damage**. The antioxidant effect of resveratrol is dependent on its non-enzymatic antioxidant action and induction of antioxidant enzymes. In this context, resveratrol elevates thiol-redox, and attenuates oxidative stress and DNA damage thus protecting heart against deleterious oxidative stress.<sup>33</sup>

Resveratrol is known to influence circulatory inflammatory biomarker levels. It increases the serum levels of anti-inflammatory adiponectin, decreases the levels of thrombogenic plasminogen activator inhibitor type 1 (PAI-1), regulates inflammation related transcription factors, reduces C-reactive protein levels, levels of atherogenic marker such as decreased oxidized low density lipoprotein, and apolipoprotein-B.<sup>34-36</sup>

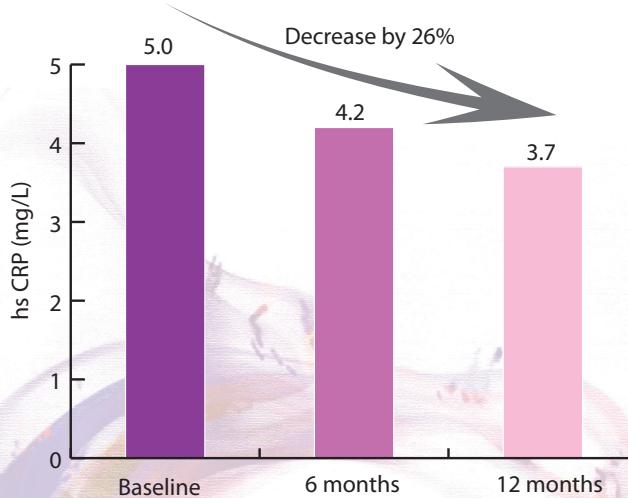
## POTENTIAL ADJUVANT USE OF RESVERATROL WITH GOLD-STANDARD THERAPIES FOR CVD

A dietary intervention with resveratrol could complement the gold standard therapy in the primary prevention of CVD. This has been substantiated in a triple-blinded, randomized, parallel, dose-response, placebo-controlled, 1-year follow-up study. In the resveratrol group high-sensitivity C-reactive protein (hs-CRP), which is a marker for predicting future risk of coronary heart disease in high risk asymptomatic individuals decreased by 26% (Figure 3). Thus, decreasing hs-CRP through complementary approaches is relevant in primary prevention. Furthermore, decrease in hs-CRP was related with decreases in TNF-α (by 19.8%) and PAI-I (by

**Long-term supplementation (1 year) of resveratrol in addition to gold standard therapy for primary prevention of CVD improves inflammatory and fibrinolytic status in high CVD risk patients**



**Figure 3** Favorable modulation of CV risk marker (hs-CRP) with resveratrol



Adapted from: Tomé-Carneiro J, González M, Larrosa M, Yáñez-Gascón MJ, García-Almagro FJ, Ruiz-Ros JA, García-Conesa MT, Tomás-Barberán FA, Espín JC. One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. *Am J Cardiol.* 2012 Aug 1;110(3):356-63.

16.8%); these markers predict onset of cardiovascular events (Table 2). TNF- $\alpha$  which modulates response to CRP is known to alter vascular endothelium homeostasis and induce plaque destabilization by increasing PAI-1 levels. Supplementation with resveratrol also helped in increasing interleukin 10, which is an anti-inflammatory marker. No adverse events were noted in the study population. The results corroborated with the fact that long-term supplementation (1 year) of resveratrol in addition to gold standard therapy for primary prevention of CVD improves inflammatory and fibrinolytic status in high CVD risk patients.<sup>37</sup>

Among constellation of benefits of resveratrol, the possibility of using it effectively along with antihypertensives such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and calcium channel blockers, and antihyperlipidemic agents such as statins appears to be promising, owing to the fact that these agents constitute as an important part of therapeutic regimen for cardioprotection and are almost always prescribed. Statins are one of the most effective measures to lower cholesterol thereby preventing atherosclerosis and reducing the incidence of coronary heart disease. However, literature is replete with evidences showing that monotherapy of statin in hypercholesterolemic state may be associated with reduced efficacy and recurrences. As a result, use of resveratrol as an adjuvant to statins to lower cholesterol

and coronary heart disease via its multitudinous actions seems rational.<sup>37,38</sup> Resveratrol has been shown to significantly decrease plasma total cholesterol, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol concentrations, apoB/apoA-I ratio, hepatic cholesterol, and triglyceride contents, and increase the plasma HDL-C concentration.<sup>39</sup>

Studies have shown that concomitant use of statins and resveratrol enhances cardioprotection. A trial compared the cardioprotective efficacy of combination therapy consisting of statin and resveratrol with individual therapies in ischemic experimental models. The experimental models were administered high cholesterol diet for 8 weeks and subsequently treated with statin and resveratrol for 2 weeks. The left ventricular recovery was remarkable in resveratrol and statin, only resveratrol and only statin recipients compared to high cholesterol no intervention. Furthermore, resveratrol and statin combination provided significant improvement in cardiac functions and lipid profile, decreased infarct size and cardiomyocyte apoptosis and increased angiogenesis. Resveratrol and statin combination rendered acute as well as chronic cardioprotection after myocardial infarction owing to its pro-angiogenic, anti-hyperlipidemic, anti-apoptotic and neo-vascularization properties.<sup>38</sup>

Moderate consumption of resveratrol rich beverages up-regulates the expression of endothelial NO synthase by activation of the metabolic sensors SIRT1 and AMP activated protein kinase (AMPK).<sup>40</sup>

Chronic administration of resveratrol has been shown to improve endothelial dysfunction related with insulin resistance syndrome. A study assessed the impact of resveratrol administration on endothelial nitric oxide synthase activity and lipid peroxidation in experimental models induced with insulin resistance syndrome. The subjects were divided into four groups; control; control plus resveratrol; fructose fed experimental models; fructose fed experimental models plus resveratrol. It was observed that resveratrol averted the development of cardiac hypertrophy, restored cardiac endothelial nitric oxide synthase

**“ Resveratrol in combination with statins renders acute as well as chronic cardioprotection after myocardial infarction owing to its pro-angiogenic, anti-hyperlipidemic, anti-apoptotic and neo-vascularization properties**



**Table 2: Inflammatory markers and plasminogen activator inhibitor type 1 levels after different interventions at baseline, 6 and 12 months**

Parameters	Timing	Placebo (maltodextrin)	A grape extract with similar polyphenolic agent without resveratrol	Resveratrol 8 mg
High-sensitivity C-reactive protein (mg/L)	Baseline	4.4 ±4.3	3.2±2.5	5.0 ±3.7
	After 6 months	4.8 ±4.1	3.2 ±2.0	4.2 ± 2.6
	After 12 months	4.8 ± 4.3	3.3±1.8	3.7±2.8
Tumor necrosis factor-alpha (pg/ml)	Baseline	13.4 ± 11.8	10.5 ± 10.6	16.2 ± 16.2
	After 6 months	12.1 ± 8.9	11.8 ± 10.4	15.2 ± 13.9
	After 12 months	12.4 ± 8.9	12.7 ± 10.9	13.0 ± 12.9
Interleukin-6 (pg/ml)	Baseline	1.6 ± 1.3	1.6 ± 1.5	1.7 ± 1.1
	After 6 months	1.7 ± 1.3	1.6 ± 1.4	1.8 ± 1.3
	After 12 months	1.8 ± 1.5	1.6 ± 1.5	1.8 ± 1.4
Interleukin-10 (pg/ml)	Baseline	9.8 ± 6.8	9.9 ± 6.2	9.6 ± 7.8
	After 6 months	9.4 ± 6.6	10.1 ± 6.5	10.6 ± 8.1
	After 12 months	8.7 ± 6.5	9.8 ± 5.9	11.5 ± 8.4
Adiponectin (µg/ml)	Baseline	14.3 ± 8.1	14.8 ± 5.9	15.4 ± 9.9
	After 6 months	14.62 ± 8.2	15.6 ± 5.7	16.8 ± 9.1
	After 12 months	14.4 ± 7.8	15.2 ± 5.3	16.4 ± 8.9
Plasminogen activator inhibitor type 1 (ng/ml)	Baseline	17.5 ± 5.2	17.1 ± 10.9	16.7 ± 6.7
	After 6 months	18.8 ± 6.9	17.9 ± 8.4	16.4 ± 7.5
	After 12 months	17.9 ± 5.9	15.5 ± 8.7	13.9 ± 5.8

**Adapted from:** Tomé-Carneiro J, González M, Larrosa M, Yáñez-Gascón MJ, García-Almagro FJ, Ruiz-Ros JA, García-Conesa MT, Tomás-Barberán FA, Espín JC. One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. Am J Cardiol. 2012 Aug 1;110(3):356-63.

activity, and controlled generation of plasma lipid peroxidation products thereby aiding in prevention of atherogenic CVDs in high-risk subjects.<sup>41,42</sup>

As discussed above, in comorbid states such as diabetes and co-existing cardiovascular disease, several intricate mechanisms work simultaneously to deteriorate functional status of an individual. Resveratrol has been appreciated for its favorable role in mitochondrial biogenesis, metabolism, content and function. The compound action of resveratrol at mitochondrial level is useful for improving insulin resistance, preventing glycemic damage to the vasculature, thwarting diabetes related CVDs and prolonging survival.<sup>43-46</sup>

The cardioprotective benefits of resveratrol due to its antioxidant potential were elucidated in a study that evaluated these properties of resveratrol extract in myocardium of diabetes

induced experimental models. Four groups each of 8 models were formed as follows: normal experimental models or control group, normal experimental models administered resveratrol, experimental subjects with diabetes, and experimental subjects with diabetes administered resveratrol. The diabetes induced experimental subjects' exemplified classical features of diabetes viz, weight loss, severe persistent hyperglycemia and increased consumption of food and water. Administration of resveratrol was useful for achieving glycemic control and normalizing final body weight. Apart from this, the serum free fatty acid levels were appreciably higher in experimental subjects with diabetes, and resveratrol helped in normalizing these levels. Resveratrol was also useful in restoring enzymatic function; pyruvate dehydrogenase activity, myocardial β-hydroxyacyl coenzyme-A dehydrogenase and citrate synthase activity. Resveratrol thus



## “ Resveratrol can function as both preventive and mitigating therapy in the management of cardiovascular diseases

contributes towards maintaining glucose homeostasis, free fatty acid oxidation, regulating myocardial metabolic enzymes and cardiac energy metabolism in diabetic state. In addition to the positive effects of resveratrol on hyperglycemia and cardiac parameters, it may favorably modify the level of biomarkers of oxidative stress. Therefore, indicating promising prospects of resveratrol supplementation in diabetes and its cardiovascular complications.<sup>40, 47</sup>

The adiponectin regulation mediated via resveratrol is proven to be protective against myocardial ischemic reperfusion injury. Resveratrol upregulates the expression of adiponectins and multimerization and thus ameliorates myocardial ischemic reperfusion injury. The effects are partly attributable to AMPK signaling.<sup>48</sup>

In myocardial infarction, the proangiogenic, and anti-apoptotic properties of resveratrol has shown promising potential. A study showed that resveratrol assuages myocardial damage by invigorating vascular endothelial growth factor-angiogenesis and tyrosine kinase receptor Flk-1.<sup>49</sup> Moreover, resveratrol is able to suppress sympathetic neural remodeling process after myocardial infarction by favorably modifying inflammatory responses and oxidative stress, thus averting the risk of arrhythmias.<sup>50</sup>

Therefore, treatment with resveratrol, which targets multiple facets of diverse cardiovascular diseases, may represent an appropriate and promising supplement to currently recommended clinical therapy and lifestyle changes. Resveratrol can function as both preventive and mitigating therapy in the management of cardiovascular diseases.<sup>13</sup>

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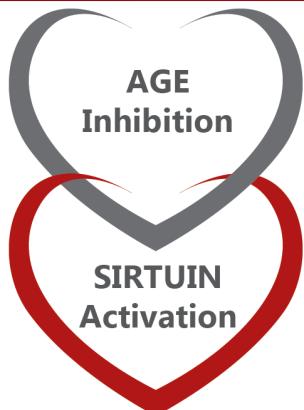
**Shifts the balance of Cardiac Metabolism from utilizing Fat to Glucose<sup>8</sup>**

*Enhances*  
**Cardiac  
Energy Output**

**Prevents Progression  
from Hypertension to  
Cardiac Failure<sup>8,15</sup>**



***Traditional treatments may not be adequate<sup>8</sup>***



- ▶ Reduces Excessive Fatty Acid Oxidation<sup>8,9</sup>
- ▶ Improves Glucose Oxidation & Energy (ATP) Output<sup>8,9</sup>
- ▶ Activates Endogenous Antioxidant Systems via Nrf2<sup>1</sup>
- ▶ Reduces Cardiac Fibrosis, Apoptosis & Cardiomyopathy<sup>8</sup>
- ▶ Improves LV Diastolic Function<sup>10</sup> & Cardiac Contractility<sup>11,12</sup>

**Enhances Myocardial Angiogenesis & Capillary density, Post MI<sup>13,14</sup>**

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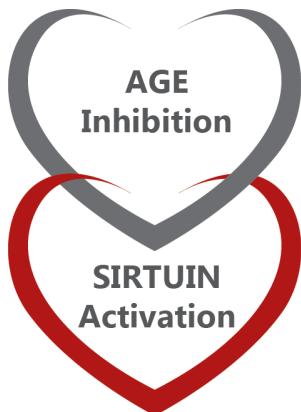
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**Prevents Progression from Hypertension to Cardiac Failure** <sup>8,15</sup>

**Aging and Diabetes are associated with marked inability of  
Mitochondria to switch from Lipid to Glucose** <sup>16</sup>



- Prevents Mitochondrial Dysfunction <sup>4</sup>
- Improves Mitochondrial Function <sup>6</sup>
- Improves Mitochondrial Biogenesis <sup>6</sup>
- Improves Cardiac Substrate Utilization <sup>9</sup>

*Additive or Synergistic effects in combination with*  
Statins, Telmisartan, Nebivolol, Perindopril, Metformin & Enalapril

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More information available on request from

**apex laboratories private limited**, SIDCO Garment Complex III Floor, Guindy, Chennai - 600 032. E-mail: aisa.cidis@apexlab.com