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Resveratrol—The "Chateau Hormone" for Cardio Diabetic Protection

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Abstract

Resveratrol is a naturally occurring phenolic compound abundantly found in grape skin and in wines. Resveratrol is a phytoalexin trans-3,5,4'-trihydroxystilbene that possesses diverse biochemical and physiological actions. It is effective in improving health and preventing or treating chronic diseases. The cardiovascular protective effects of Resveratrol suggest the anti-atherogenic and anti-inflammatory activity of the compound on endothelial cells. Resveratrol attenuates myocardial ischemic reperfusion injury, atherosclerosis and reduces ventricular arrhythmias. Resveratrol has been widely studied and is shown to have anti-oxidant, anti-inflammatory, anti-proliferative and anti-angiogenic effects and many signalling pathways are among the molecular targets of Resveratrol. Based on these mechanistic considerations, the involvement of Resveratrol has been observed in cardiovascular diseases, cancer and neurodegenerative diseases. In type 2 diabetes patients, when Resveratrol was given along with anti-diabetic agents, it was found to lower blood glucose, HbA1C and increase the insulin sensitivity and the levels of HDL-C. Resveratrol acts on the SIRT1 gene and stimulates endogenous pathways to promote health and longevity.

Keywords

Resveratrol, Cardiovascular Disease, Atherosclerosis, HDL-C, Diabetes, *β*-Blockers, Residual Vascular Risk

1. Introduction

Resveratrol was first isolated in 1939 from the root of white hellebore, *Veratrum grandiflorum*. The name Res-

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veratrol was derived from this source since it is a resorcinol derivative from a Veratrum species. Resveratrol is a stilbenoid produced by 72 different plant species, especially grapevines, pines, legumes, peanuts, soya beans and pomegranates in high concentrations. In particular, a fungal infection of Botrytis cinerea in grapes leads to exclusive synthesis of Resveratrol in the leaf epidermis and grape skin [1]. Resveratrol is termed as the "Chateau Hormone" as Resveratrol is found in abundance in the grapes that are grown in the vineyards attached to magnificent French Chateaus or villas. Resveratrol is not a hormone in the true sense. But, Resveratrol acts like a hormone by exercising its effects on various organ systems. It has effects on various organs, organ systems or tissues like the cardiovascular system, blood sugar, vascular endothelium, different types of tumors and inflammatory mediators. The "French Paradox" in 1992 is based on the epidemiological data from French people who had a low incidence of coronary heart disease, despite consumption of high saturated fat diet. This was explained by their regular consumption of red wine. Resveratrol is said to be the major bioactive component of red wine. Resveratrol is known to have cardioprotective and anti-diabetic activity. Resveratrol's health effects can be summarized as scavenging intracellular reactive oxygen species, inhibiting the oxidation of low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), preventing platelet aggregation, suppressing smooth muscle cell proliferation, inducing apoptotic cell death through activation of mitochondria dependent pathways, exhibiting anti-inflammatory activity via down-regulation of proinflammatory cytokines, promoting cell differentiation and acting via SIRT1 gene and increasing longevity and promoting healthy ageing [2] [3]. Resveratrol acts through plethora of activities (**Figure 1**), and reinforces the notion that CVD death may be independently modulated by diet-based strategies that includes use of Resveratrol.

2. Resveratrol: The Conduit That Provides Cardioprotection

Cardiovascular disease (CVD) is a major cause of morbidity and mortality throughout the world and atherosclerosis of the major arteries is the most frequently reported cause. A progressive decline in CVD related mortality over the past few decades has been reported worldwide due to advances in anti-CVD strategies and also due to the discovery of dietary agents with cardioprotective activities.

2.1. Resveratrol: Provides Vasoprotection in Atherosclerosis

Atherosclerosis is a disease of the arterial intima caused by the retention of modified LDL-C, hemodynamic and reductive-oxidative stress leading to accumulation of lipids and fibrous elements in the arteries. Progression of atherosclerosis is characterized by atheroma instability and plaque disruption followed by local thrombosis, which constitute the clinical indications of acute coronary syndrome. Resveratrol exerts diverse biological actions on both progression and regression of atherosclerosis (**Figure 2**) [4]. One of the vital functions of endothelial cell is to maintain equilibrium between vasodilators, like nitric oxide (NO) and vasoconstrictors, such as endothelin-1 (ET-1). Their co-operation provides endothelial cell wall thromboresistance and prevents atherogenesis. Recent evidences showed that, Resveratrol has the ability to regulate the production of these vasodilators and vasoconstrictors. Resveratrol increases the expression in human vascular endothelial cells of endothelial nitric oxide synthase (eNOS). Resveratrol potentially inhibits stress induced ET-1 gene expression and ET-1 mRNA [5]. Thus by increasing NO and by decreasing the ET-1 level, Resveratrol improves endothelial function. Oxidized LDL-C also contributes to the progression of the early lesion by itself stimulating endothelial cells to produce pro-inflammatory molecules, which lead to the recruitment of further immune cells. Activated endothelial cells upregulate adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular cell

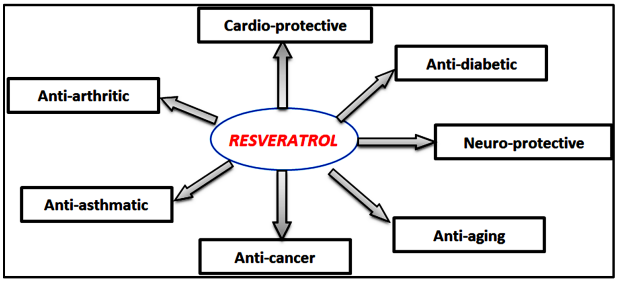

Figure 1. Physiological effects of Resveratrol.

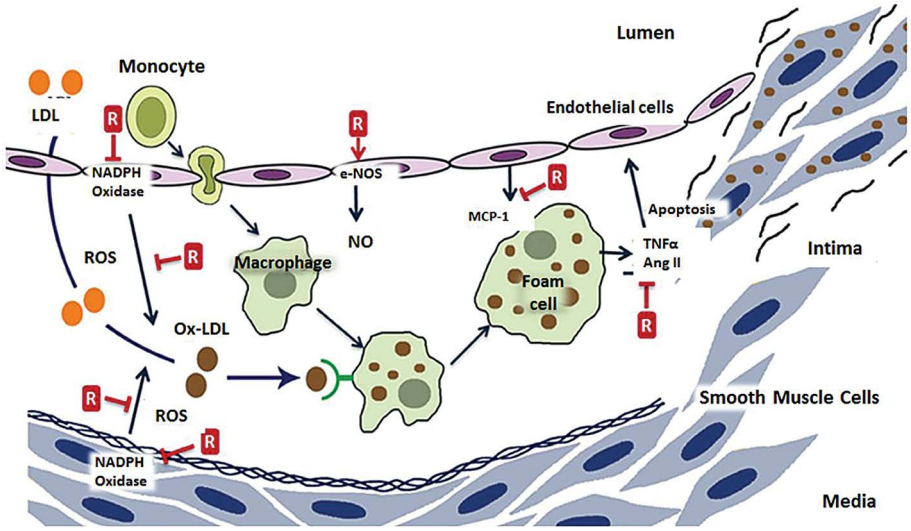

Figure 2. Role of Resveratrol (R) in atherosclerosis.

adhesion molecule-1 (VCAM-1) and endothelial-leukocyte adhesion molecule-1 (E-selectin) on their cell surface facilitating transmigration of further leukocytes. The inflammatory environment within the lesion leads to the migration and proliferation of smooth muscle cells, infiltration of immune cells including B-cells, dendritic cells, mast cells and T-cells as well as elaboration of a collagen-rich matrix. The advanced lesion consists of a core containing foam cells, lipids and necrotic debris, which is surrounded by smooth muscle cells. The growth is asymmetrical protruding into the lumen and resulting in further blood flow changes. The exact composition of the plaque dictates the stability of the plaque. The fibrous cap, which is produced by smooth muscle cells and influenced by immune cells, prevents the contact between blood components and pro-thrombotic material within the lesion. Thrombus formation occurs once the fibrous cap ruptures and coagulation factors come into contact with contents of the lesion.

Resveratrol reduces the expression of adhesion molecules like VCAM-1, ICAM-1 and E-selectin and helps reduce progression of plaque formation. Due to the antioxidant activity of Resveratrol there is reduction in lipid peroxidation, apoptotic cell death and expression of inflammatory mediators; thus providing cardioprotection (**Figure 3**). Inflammation mediates all stages of atherosclerosis from initiation to progression and eventually, plaque rupture. Prostaglandin E2 (PGE2) plays a key role in inflammation; its synthesis is catalyzed by an enzyme cyclooxygenase-2(COX-2). Resveratrol inhibits COX-2 activity and regulates its transcription and expression, thereby inhibiting the production of PGE2. Resveratrol inhibits Interleukin-6 (IL-6) and Interleukin-8 (IL-8) which are circulating cytokines. Also, Resveratrol inhibits granulocyte macrophage colony-stimulating factor, which is an important factor mediating inflammation [6] [7].

Oxidation of LDL-C is an important cause of endothelial injury and induction of expression of pro-inflammatory molecules in endothelial cells in atherosclerosis. High levels of plasma LDL-C are associated with increased risk of atherosclerosis and removal of LDL-C is important for the treatment of inflammatory response. Resveratrol was found to protect lipids from peroxidative degradation and inhibit the uptake of oxidized LDL-C in the vascular wall [8]. After injury to endothelial cells, platelets aggregate and adhere to the injured cell surface, thus initiating the process of thrombus formation. This plays a critical role in the development and progression of atherosclerosis (**Figure 4**). Deposited platelets release platelet-derived growth factor, which triggers the migration and proliferation of smooth muscle cells leading to progression of atherosclerosis. Resveratrol blocks platelet aggregation by inhibiting the adhesion of collagen with platelets, the first step of platelet activation and preclinical studies have showed antiplatelet actions of Resveratrol. The mechanism for this protective effect of Resveratrol is attributed to its COX-1 inhibition activity. Thromboxane A2 (TXA2), which is synthesized by COX-1 in platelets, is a potent inducer of platelet aggregation and a vasoconstrictor [9].

In vitro studies showed that Resveratrol significantly inhibits collagen induced platelet aggregation as well as adenosine diphosphate (ADP)-induced platelet aggregation in a concentration dependent manner. *In vivo* studies showed that Resveratrol inhibits ADP-induced platelet aggregation [10].

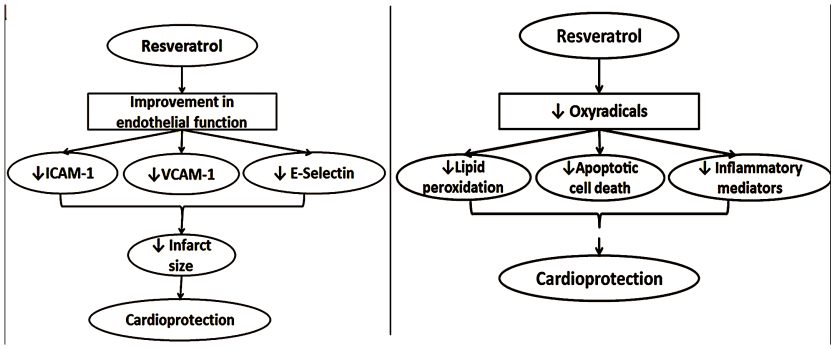

Figure 3. Resveratrol provides cardioprotection.

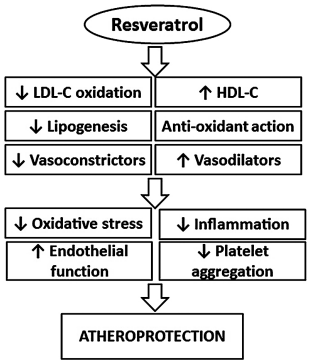

Figure 4. Resveratrol provides atheroprotection.

Acute myocardial infarction (AMI) is the most common type of cardiovascular disease with a high mortality and morbidity. Fundamentally, AMI leads to the death of cardiomyocytes. One of the most important factors responsible for the poor recovery of AMI is ischemia/ reperfusion (I/R) injury occurring during the treatment, which leads to necrosis of the cardiomyocytes and weakens the effect of reperfusion therapy. Resveratrol reduces I/R injury by reducing intracellular calcium level so that myocardial apoptosis triggered by calcium overload is reduced, Resveratrol also provides cardioprotection by enhancing eNOS activity [11]. Animal studies showed that preinfusion of Resveratrol is effective to prevent reperfusion induced arrhythmias and mortality. This protective effect on ventricular arrhythmias and cardiac cell damage by Resveratrol is associated with its antioxidant activity and enhanced NO release during the reperfusion period [12].

2.2. Resveratrol: Lowers Cholesterol and Triglycerides

Abnormal lipid profile is one of the important risk factor for various cardiovascular diseases and associated morbidity and mortality. A number of therapeutic agents have been investigated for their efficacy in lowering LDL-C and augmenting the levels of HDL-C. Resveratrol has shown to reduce the secretion of very low density lipoprotein cholesterol (VLDL-C) from the liver which in turn transforms into LDL-C in the circulation. Research has also found that Resveratrol activates the Peroxisome Proliferator Activated Receptor-alpha (PPAR-α) receptors, which are associated with increase in the HDL-C levels. Thus, Resveratrol significantly increases the level of plasma HDL-C and on the other hand, it reduces total cholesterol and LDL-C. Because of these effects, Resveratrol reduces the formation of atherosclerotic plaques in an animal study [13].

Recent evidences state that Resveratrol is beneficial for metabolic and cardiovascular health and increases life expectancy of CVD patients. Resveratrol decreases platelet aggregation, promotes vasorelaxation, suppresses atherosclerosis and reduces lipid peroxidation. Additionally, Resveratrol reduces triglyceride (TG), LDL-C, total cholesterol and increases HDL-C significantly.

An Indian study [14] has shown that Resvita capsule containing Resveratrol (5 mg) along with Proanthocyanidins, Omega-3 fatty acids and minerals was found to be beneficial in hyperlipidemic patients. After 12 weeks of treatment the results obtained were as follows.

There was considerable reduction in atherogenic lipids including triglycerides, total cholesterol, LDL-C and VLDL-C. The treatment led to 25.63% increase in HDL-C.

Initially mean value of LDL-C: HDL-C (3.64) and total cholesterol (TC): HDL-C (5.26) were high but after the treatment, mean value of LDL-C: HDL-C (3.43) and TC: HDL (3.80) decreased significantly ($p < 0.05$) as shown in **Figure 5**.

After the Resveratrol treatment, there was significant improvement in all efficacy variables over the baseline values of each parameter studied. The mean percentage change in all lipid parameters is as shown in **Figure 6**. Adverse events included headache and nausea which were mild and seen in 2 patients [14].

This study shows that Resveratrol has a beneficial role to play in hyperlipidemic patients.

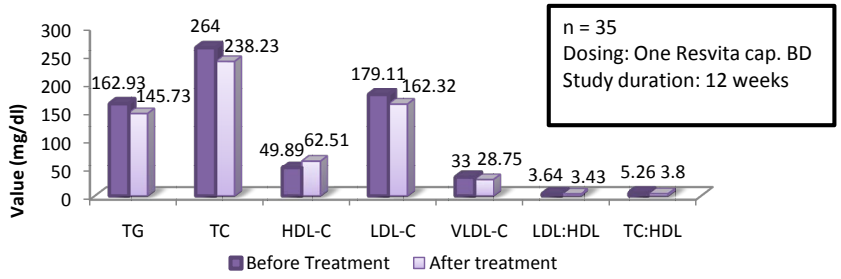

Figure 5. Resveratrol improves the lipid profile.

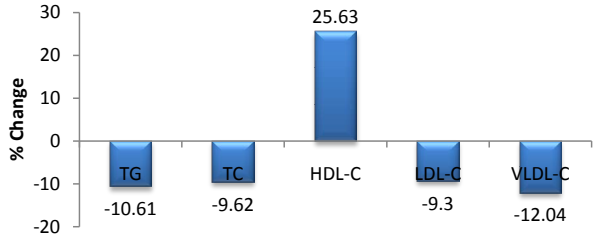

Figure 6. Resveratrol increases HDL-C.

3. Resveratrol: An Add on Therapy in Diabetes

Diabetes Mellitus (DM) is a metabolic disorder that is rapidly reaching epidemic proportions. The World Health Organization (WHO) has predicted that by 2025, 300 million people will be diabetic worldwide. DM eventually leads to diseases of the coronary arteries and the cerebrovascular system. Also DM in its course may cause renal failure, blindness, neurological complications or premature death [15]. Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia and high incidences of vascular complications, oxidative stress and disturbances in the lipid metabolism. Resveratrol has received considerable attention of the research community for its wide range beneficial effects that include antidiabetic activity.

Several mechanisms have been implicated in increasing the oxidative stress in overt DM. The eNOS (endothelial nitric oxide synthase) plays a fundamental role in endothelial-dependent vasodilation via the synthesis of NO (Nitric Oxide). Various preclinical and clinical studies have shown a correlation between lack of eNOS activation and consequent abnormalities that can contribute to enhanced insulin resistance. Resveratrol improves endothelial dysfunction by increasing NO production; it also increases the expression of eNOS gene in the endothelial cells and thus reduces insulin resistance. Multiple mechanisms have been proposed to explain the anti-inflammatory and insulin-sensitizing effects of Resveratrol [16].

Resveratrol activates Sirtuin1 (Silent information regulator T1), a protein which regulates important biological pathways in human body. Sirtuin1 regulates the biogenesis of mitochondria in the liver and muscle, as it increases the oxidative phosphorylation via the deacetylation of peroxisome proliferator-activated receptor-γ co-activator PGC-1α (PPAR-γ coactivator 1-alpha). PGC-1α is a transcriptional coactivator that regulates the genes involved in energy metabolism. Sirtuin1 induces the mobilization of lipids in the adipose tissue by inhibiting adipogenesis and activating lipolysis, and also protects pancreatic β-cells against hyperglycemia-induced oxidative stress. In addition, Sirtuins in the pancreas also stimulates the glucose-induced secretion of insulin by β-cells. Furthermore, activation of Sirtuin1 increases the synthesis of adiponectin, which is known to improve sen-

sitivity to insulin. The Sirtuin1 induced activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway has also shown to mediate the beneficial metabolic effects of Resveratrol. Activation of AMPK in skeletal muscle increases the insulin sensitivity as shown in **Figure 7** [17].

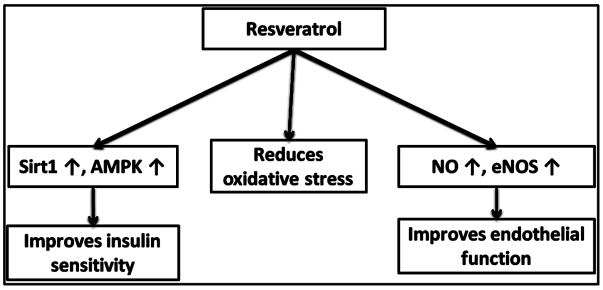

Figure 7. Resveratrol in diabetes mellitus.

In a double-blind, placebo-controlled study, effects of Resveratrol on insulin sensitivity in male patients with type 2 diabetes was evaluated. It was found that oral Resveratrol in reasonably low dosage (2 × 5 mg daily) improved insulin sensitivity and, as a consequence, decreased blood glucose levels and delayed the appearance of glucose peaks after a test meal. In addition, studies document that Resveratrol decreases oxidative stress [16].

Another preclinical study has shown that Resveratrol prevents diabetic nephropathy by inducing the phosphorylation of AMPK and activation of SIRT1-PGC-1α signaling, which appear to prevent lipotoxicity-related apoptosis and oxidative stress in the kidney [18].

4. Resveratrol: Overcomes the Limitations of β-Blockers in Hypertensives

β-blockers are one of the agents of choice to treat hypertension. ß-blockers offer significant advantages in the treatment of several forms of heart disease; however they have adverse effects on the lipid profile. The β-blockers which are known to decrease HDL-C and increase triglycerides are Atenolol, Bisoprolol, Metoprolol and Propanolol. Metoprolol is a widely used antihypertensive drug, which reduces or inhibits the agonistic effect of catecholamines on the heart. This means that the usual increase in heart rate, cardiac output, cardiac contractility and blood pressure, produced by the acute increase in catecholamines, is reduced by Metoprolol. The effects of ß-blockers including Metoprolol on blood lipids have been studied extensively. The catecholamines inactivate lipoprotein lipase, an enzyme involved in the metabolism of triglycerides to free fatty acids. Another hypothesis states that, while the β-receptors are blocked, the α-receptors get stimulated and they play a role in inhibiting lipoprotein lipase. Incidentally this enzyme also catalyzes the conversion of triglycerides to HDL-C [19]. This therefore leads to an increase in triglycerides and decrease in the HDL-C levels.

A clinical study carried out for the duration of 12 months concluded that treatment with Metoprolol is associated with 14% increase in total triglycerides and 13% decrease in HDL-C [19]. Short duration treatment of Metoprolol as less as 16 days is also associated with reduction in HDL-C cholesterol [20]. Co-administration of Resveratrol with Metoprolol seems the most plausible approach to counteract this decrease, as Resveratrol increases the HDL-C levels as mentioned in the above study [14].

5. Resveratrol Increases HDL-C: Molecular Mechanism

HDL-C exerts its anti-atherogenic properties primarily by facilitating the efflux of cholesterol from peripheral tissues and transporting it back to the liver by a process called reverse cholesterol transport.

Paraoxonase-1 (PON1) is an enzyme associated with HDL-C which is secreted by the liver. PON1 has anti-oxidative properties, which are associated with the enzyme's capability to decrease oxidative stress in atherosclerotic lesions and to attenuate the development of atherosclerosis. Epidemiological evidences demonstrate low PON1 activity with increased risk of cardiovascular events and PON1 is an independent risk factor for coronary artery disease. Therefore, pharmacological modulation of PON1 activity or PON1 gene expression constitutes a useful approach for preventing atherosclerosis [21].

Oxidation of HDL-C results in the loss of its beneficial anti-oxidant and anti-inflammatory effects. PON1 prevents HDL-C from oxidation, thus preserving its beneficial actions. PON1 also prevents the oxidation of LDL-C,

a critical step in atherosclerotic plaque formation. Thus by preventing oxidation of HDL-C and LDL-C, PON1 prevents atherosclerosis.

Low activity of PON1 has been reported in disease conditions that include renal disease, diabetes, HDL-C deficiencies and liver cirrhosis. Resveratrol increases PON1 gene expression in human hepatocytes primary cultures, and thereby increases HDL-C levels [22].

6. Resveratrol: Targets Residual Vascular Risk in CVD Patients

Residual Vascular Risk is defined as the risk of macrovascular events and microvascular complications that persist in patients despite current standards of care, including achievement of LDL-C goals, control of blood pressure and blood glucose (in case of diabetic patients). A recent meta-analysis of statin trials showed that reduction of LDL-C by 39 mg/dl, reduces the relative risk of major coronary events by 23%, but it leaves a significant (77%) unaddressed cardiovascular residual risk (**Figure 8**) [23]. Resveratrol has several properties believed to be beneficial in terms of Residual Vascular Risk reduction in CVD patients on statins. Resveratrol regulates SIRT1 dependent cholesterol metabolism by deacetylating and activating Liver X receptor alpha (LXRα), a critical nuclear receptor that controls cholesterol, lipid homeostasis and early step of HDL-C biogenesis. Through this mechanism Resveratrol increases HDL-C cholesterol.

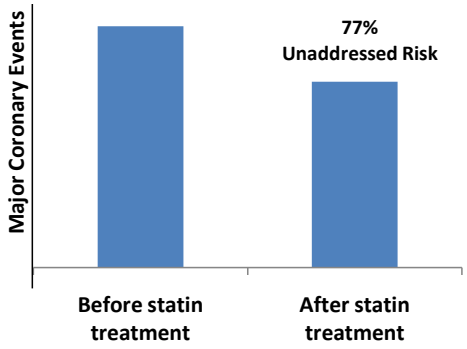

Figure 8. Residual risk despite lowering of LDL-C by 39 mg/dl.

Additionally, Resveratrol has shown to decrease platelet aggregation, promote vasorelaxation, suppress atherosclerosis and reduce lipid peroxidation. Thus, besides reducing the LDL-C levels, Resveratrol treatment is associated with reduction in total serum cholesterol concentration, TG, VLDL-C and significant elevation in HDL-C levels.

7. Conclusion

Resveratrol, the "Chateau Hormone" provides cardioprotection by acting on the mediators that initiate atherosclerosis. Also, it increases the levels of HDL-C and improves the lipid profile. Resveratrol is found to be beneficial in type 2 DM because of its antioxidant, anti-inflammatory properties and has favorable effects on insulin sensitivity. Resveratrol decreases Residual Vascular Risk in CVD patients on statins.

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