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RESEARCH ARTICLE

A REVIEW ON BENEFITS OF RESVERATROL ON HEALTH AND DISEASES ESPECIALLY CARDIOVASCULAR DISEASES

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ABSTRACT

Resveratrol, a phenolic compound found in various plants, including grapes, red wine and resveratrol enriched supplements show promising results in the treatment of cancer, obesity, type 2 diabetes, and cardiovascular diseases. Resveratrol can promote transcription factor nuclear factor-erythroid 2- related factor 2 (Nrf2) activation, increase the expression level of SIRT-1, which is a sirtuin family protein, and reduce mTOR pathway signalling. This compound has anti-inflammatory properties in that it inhibits or antagonizes the nuclear factor-κB (NF-κB) activity, which is a redox-sensitive transcription factor that coordinates the inflammatory response. Inflammation and oxidative stress, which are common features in patients with cardiovascular disease, cancer and neurological disorders and thus SIRT-1 helps in the prevention of such diseases. Resveratrol might also act as an antioxidant and help in anti-aging, and control of cell cycle and apoptosis. Many research studies have suggested that consumption of 250-400ml red wine per day is beneficial in the prevention of many disease conditions especially cardiovascular diseases.

INTRODUCTION

Resveratrol and Its Role In Diseases

Resveratrol (RS) (3, 5, 4'-trihydroxy-trans-stilbene) belongs to a class of polyphenolic compounds called stilbene. Some types of plants produce resveratrol and other stilbene in response to stress, injury and fungal infection. Its presence was first reported in red wine leading to speculation that resveratrol might explain the "French Paradox". More recently, reports on the potential for resveratrol to inhibit the development of cancer and cardiovascular diseases (CVD) have continued to generate scientific interest (1, 2, 3&4). Resveratrol has also been shown to offer protection against ischemic injuries (5), obesity (6) and diabetes (7). The objective of this review was to critically examine the results from recent research concerning potential effect of RS in various disease conditions especially CVD.

Food Sources of Resveratrol

Resveratrol is found in grapes, wine, grape juice, peanuts, and berries of Vaccinum species, including blueberries, bilberries, and cranberries. In grapes, resveratrol is found only in the skins. The amount of resveratrol in grape skins varies with the grape cultivar, its geographic origin, and exposure to fungal infection. The amount of fermentation time a wine spends in contact with grape skins is an important determinant of its resveratrol content (8).

Table 1 Total resveratrol contents of wine and grape juice

Beverage	Total resveratrol (mg/liter)	Total resveratrol in a 5-oz glass (mg)
White wines (Spanish)	0.05-1.80	0.01-0.27
Rosé wines (Spanish)	0.43-3.52	0.06-0.53
Red wines (Spanish)	1.92-12.59	0.29-1.89
Red wines (global)	1.98-7.13	0.30-1.07
Red grape juice (Spanish)	1.14-8.69	0.17-1.30

Table 2 Total resveratrol content of selected foods

Food	Serving	Total resveratrol (mg)
Red Grapes	1cup(160g)	0.24-1.25
Peanuts(raw)	1cup(146g)	0.01-0.26
Peanuts(boiled)	1cup(180g)	0.32-1.28
Peanut Butter	1cup(258g)	0.04-0.13

(Hidjon J *et al*,2008)

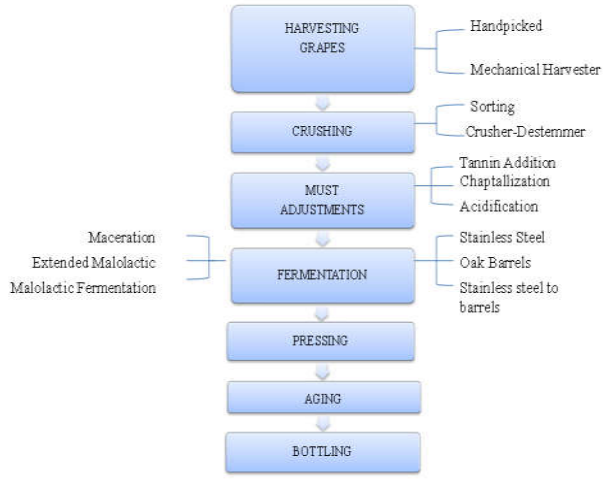

Fig 1 Process of Preparing Red Wine

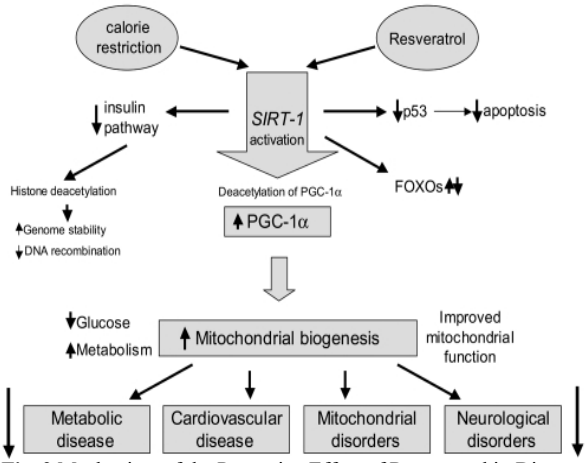

Fig. 2 Mechanism of the Protective Effect of Resveratrol in Disease Conditions

Fig.2 shows SIRT-1 activation pathways**:** Resveratrol and calorie restriction activate similar *SIRT-1*–mediated pathways whose actions result in prevention of common age-related diseases.

Resveratrol can promote transcription factor nuclear factor-erythroid 2- related factor 2 (Nrf 2) activation, increase the expression level of SIRT-1, which is a sirtuin family protein, and reduce mTOR pathway signaling.This compound has anti-inflammatory properties in that it inhibits or antagonizes the nuclear factor-*κ* B (NF-*κ*B) activity, which is a redox-sensitive transcription factor that coordinates the inflammatory response. Inflammation and oxidative stress, which are common features in patients with cardiovascular disease and cancer and SIRT-1 due to its anti-inflammatory function may help to prevent or aggravate inflammation. Resveratrol might also act as an antioxidant and help in anti-aging, and control of cell cycle and apoptosis.

An early target of resveratrol is the sirtuin class of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases. Seven sirtuins have been identified in mammals, of which *SIRT-1* is believed to mediate the beneficial effects on health and longevity of both calorie restriction and resveratrol. A number of intracellular pathways are activated by *SIRT-1*. The extent to which the sirtuin-activating actions of resveratrol are direct or indirect is still not resolved completely. The pathways regulated by sirtuins include gluconeogenesis and glycolysis in the liver, fat metabolism, and cell survival. Depending on cell type and circumstances, sirtuins activate or suppress members of the forkhead box O (FOXO) group of transcription factors. FOXOs then activate or suppress specific genes, leading to a decrease in apoptosis, an increase in antioxidant activities, DNA protection, anti-inflammatory effects, and modulation of various other mechanisms so as to promote the health of the cell and thus the organism. Several reports have presented evidence that *SIRT-1* interacts directly and deacetylates the metabolic regulator and transcriptional coactivator, peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α). By doing so it improves mitochondrial function, induces genes for mitochondrial and fatty acid oxidation and increases mitochondrial membrane potential. Thus SIRT-1 plays an important role in prevention of Metabolic, cardiovascular, Mitochondrial and Neurological diseases through its anti-inflammatory and antioxidant properties (9).

Benefit of Resveratrol Intake in Cardiovascular Diseases

- According to WHO CVDs are the number one causes of death globally: more people die annually from CVDs than from any other cause (17). An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke (17). Low- and middle-income countries are disproportionally affected: over 80% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women (18). The number of people who die from CVDs, mainly from heart disease and stroke, will increase to reach 23.3. million by 2030. CVDs are projected to remain the single leading cause of death (19).

The French Paradox

The term French paradox was coined in 1992 to describe the relatively low incidence of cardiovascular disease in the French population and despite a relatively high dietary intake of saturated fats, and potentially attributable to the consumption of red wine. After about 20 years, several studies have investigated the fascinating, overwhelmingly positive biological and clinical associations of red wine consumption with cardiovascular disease and mortality. Light to moderate intake of red wine produces a kaleidoscope of potentially beneficial effects that target all phases of the atherosclerotic process, from atherogenesis (early plaque development and growth) to vessel occlusion (flow-mediated dilatation, thrombosis). Such beneficial effects involve cellular signaling mechanisms, interactions at the genomic level, and biochemical modifications of cellular and plasma components. Red wine components, especially alcohol, resveratrol, and other polyphenolic compounds, may decrease oxidative stress, enhance cholesterol efflux from vessel walls (mainly by increasing levels of high-density lipoprotein cholesterol), and inhibit lipoproteins oxidation, macrophage cholesterol accumulation, and foam-cell formation. These components may also increase nitric oxide bioavailability, thereby antagonizing the development of endothelial dysfunction, decrease blood viscosity, improve insulin sensitivity, counteract platelet hyperactivity, inhibit platelet adhesion to fibrinogen-coated surfaces, and decrease plasma levels of von Willebrand factor, fibrinogen, and coagulation factor VII. Light to moderate red wine consumption is also associated with a favourable genetic modulation of fibrinolytic proteins, ultimately increasing the surface-localized endothelial cell fibrinolysis. Overall, therefore, the ‘‘French paradox’’ may have its basis within a milieu containing several key molecules, so that favourable cardiovascular benefits might be primarily attributable to combined, additive, or perhaps synergistic effects of alcohol and other wine components on atherogenesis, coagulation, and fibrinolysis. Conversely, chronic heavy alcohol consumption and binge drinking are associated with increased risk of cardiovascular events. Although mounting evidence strongly supports beneficial cardiovascular effects of

Table 3 published clinical studies dealing with the effects of resveratrol on health.

Objective	Sample characteristics	Trial design, resveratrol dose and time of intervention	Conclusion	Reference
To test whether supplementation of resveratrol would enhance memory performance in older adults.	Overweight Old Subjects. (n=46) (Female-18; Male-28) Age=51-75yrs	23 healthy overweight older individuals that successfully completed 26 weeks of resveratrol intake (200 mg/d) were pairwise matched to 23 participants that received placebo Before and after the intervention/control period, subjects underwent memory tasks and neuroimagingto assess volume, microstructure, and functional connectivity (FC) of the hippocampus, a key region implicated in memory functions In addition to this anthropometry, glucose and lipid metabolism, inflammation, neurotrophic factors, and vascular parameters were assayed	Resveratrol improves memory performance in association with improved glucose metabolism and increased hippocampal FC in older adults. The findings offer the basis for novel strategies to maintain brain health during aging.	(10)
To assess intestinal and hepatic lipoprotein turnover, in humans, after 2 weeks of treatment with resveratrol or placebo.	Overweight or Obese individuals with mild hyper triglyceridemia (n=8) (Male-8) Age=28-55yrs	Subjects were studied on 2 occasions, 4 to 6 weeks apart, after treatment with resveratrol (1000 mg daily for week 1 followed by 2000 mg daily for week 2) or placebo in a randomized, double-blinded, crossover study. Steady state lipoprotein kinetics was assessed in a constant fed state with a primed, constant infusion of deuterated leucine.	2 weeks of high-dose resveratrol reduces intestinal and hepatic lipoprotein particle production by reducing the production rate of intestinal apoB-48Containing chylomicrons) and hepatic apoB-100(containing VLDL) that lead to hypertriglyceridemia and thus prevent obesity.	(11)
To investigate if there are Calorie restriction-like effects of resveratrol supple-mentation on energy metabolism and metabolic profile in obese humans	Healthy Obese Individuals (n=11) (Male=11) Age=50-55yrs	Healthy, obese men with placebo were treated with150 mg/day resveratrol (resVida) in a randomized double-blind crossover study for 30 days. To confirm systemic conversion of resveratrol to dihydroresveratrol (DHR), total (sum of conjugated and unconjugated resveratrol) and free plasma levels of both compounds were analyzed each week during the 30-day period of resveratrol or placebo supplementation.	30 days of resveratrol supplementation induces metabolic changes in obese humans, mimicking the effects of calorie restriction.	(12)
To determine whether trans-resveratrol had a dose-related effect on DNA methylation and prostaglandin expression in humans	Adult women at risk of breast cancer. (n=39) (Female=39) Age= all age groups	In double-blind fashion to placebo, 5 or 50 mg transresveratrol twice daily for 12 wk. Methylation assessment of 4 cancer-related genes (p16, RASSF-1α, APC, CCND2) was performed on mammary ductoscopy pecimens.	The effects of trans-resveratrol on the breast of women at increased breast cancer risk include a decrease in methylation of the tumor suppressor gene RASSF-1α.Thus helping in the prevention of cancer.	(13)
To measure concentrations of resveratrol and its metabolites in colorectal tissue of humans who ingested resveratrol.	Colorectal Cancer patients. (n=20) (Female=11;Male-9) Age=46-83yrs	Subjects consumed 8 daily doses of resveratrol at 0.5 or 1.0g prior to surgical resection. Parent compound plus its metabolites resveratrol-3-O-glucuronide, resveratrol-4′-O-glucuronide, resveratrol-3-O-sulfate, resveratrol-4′-O-sulfate, resveratrol sulfate glucuronide and resveratrol disulfate were identified by high pressure liquid chromatography (HPLC) with UV or mass spectrometric detection in colorectal resection tissue. Cell proliferation, as reflected by Ki-67 staining, was compared in pre- and post-intervention tissue samples.	Consumption of daily oral doses of resveratrol at 0.5 or 1.0g produce levels in the human GI tract of an order of magnitude sufficient to elicit anti-carcinogenic effects.	(14)
To determine whether or not resveratrol would inhibit cytokine release in vitro by alveolar macrophages from patients with COPD.	Cigarette smokers (15no.) and patients with COPD (15no.) (n =30) (Female-7; Male-23) Age=54-68yrs	Alveolar macrophages were isolated from bronchoalveolar lavage (BAL) fluid from both the groups). The macrophages were stimulated with either interleukin (IL)-1b or cigarette smoke media (CSM) to release IL-8 and granulocyte macrophage-colony stimulating factor (GM-CSF). The effect of resveratrol was examined on both basal and stimulated cytokine release.	Resveratrol inhibits inflammatory cytokine release from alveolar macrophages in COPD by inhibiting basal release of IL-8 and GM-CSF which are released in increased amounts in COPD and thus protecting against COPD.	(15)
To assess the clinical efficacy of nutritional amounts of grape polyphenols (PPs) in counteracting the metabolic alterations of high-fructose diet, including oxidative stress and insulin resistance (IR), in healthy volunteers with high metabolic risk.	Overweight/obese first-degree relatives of type 2 diabetic patients. (n=38) (Female-20;Male-18) Age=30-65yrs	Patients were randomized in a double-blind controlled trial between a grape PP (2 g/day) and a placebo (PCB) group. Subjects were investigated at baseline and after 8 and 9 weeks of supplementation, the last 6 days of which they all received 3 g/kg fat-free mass/day of fructose. The primary end point was the protective effect of grape PPs on fructose-induced IR.	A natural mixture of grape PPs at nutritional doses efficiently prevents fructose-induced oxidative stress and IR. Thus 9 weeks of supplementation with nutritional doses of grape PPs protects against fructose-induced oxidative stress and IR.	(16)

Table 4 Published clinical studies dealing with the effects of resvearterol on cardiovascular diseases

Objective	Sample Characteristics	Trial design, resveratrol dose and time of intervention	Conclusion	Reference
To investigate whether Resveratrol(RES) has a clinically measurable cardioprotective effect in patients after myocardial infarction	Post Infarct Caucasian patients. (n=40)	It was a double-blind, placebo controlled trial where patients were randomized into two groups. One group received 10 mg RES capsule daily for 3 months. Also Systolic and diastolic left ventricular function, flow-mediated vasodilation (FMD), several laboratory and hemorheological parameters were measured before and after the treatment.	Resveratrol improved left ventricle diastolic function, endothelial function, lowered LDL-cholesterol level and protected against unfavourable hemorheological changes measured in patients with coronary artery disease (CAD).	(22)
To investigate the effect of a grape supplement containing 8 mg resveratrol in oxidized LDL (LDLox), apolipop- rotein-B (ApoB), and serum lipids on statin-treated patients in primary cardiovascular disease prevention (PCP).	Patients (n=75)	A triple-blind, randomized, placebo-controlled trial was conducted,where 75 patients (three parallel arms) consumed one capsule (350 mg) daily for 6 months containing resveratrol-enriched grape extract (GE-RES, Stilvid®), grape extract (GE, similar polyphenolic content but no resveratrol), or placebo (maltodextrin).	In the GE-RES group there was a decrease in the LDLc, ApoB, LDLox and LDLox/ApoB decreased. Thus GE-RES reduced atherogenic markers and might exert additional cardioprotection beyond the gold-standard medication in patients from PCP. The presence of resveratrol in the GE was necessary to achieve these effects.	(23)
To investigate dose-depending effects of a resveratrol-containing grape supplement on stable patients with coronary artery disease (CAD)	Stable-CAD patients. (n-75) (Male-64, Female-11) Age=18-80yrs	A triple-blind, randomized, placebo-controlled, one-year follow-up, 3-arm pilot clinical trial, patients received 350 mg/day of placebo, resveratrol-containing grape extract (grape phenolics plus 8 mg resveratrol) or conventional grape extract lacking resveratrol during 6 months, and a double dose for the following 6 months. Changes in circulating inflammatory and fibrinolytic biomarkers were analyzed. Moreover, the transcriptional profiling of inflammatory genes in peripheral blood mononuclear cells (PBMCs) was explored using microarrays and functional gene expression analysis.	Chronic daily consumption of a resveratrol-containing grape nutraceutical could exert cardiovascular benefits in stable-CAD patients by increasing serum adiponectin, preventing plasminogen activator inhibitor type1 (PAI-1) increase and inhibiting atherothrombotic signals in peripheral blood mononuclear cells (PBMCs).	(24)
To investigate the effects of a dietary resveratrol-rich grape supplement on the inflammatory and fibrinolytic status of subjects at high risk of CVD.	Patients undergoing primary prevention of CVD. (n=75) (Male-34; Female-41) Age=18-80yrs	A triple-blinded, randomized, parallel, dose-response, placebo-controlled, 1-year follow-up trial was conducted where patients allocated in 3 groups, consumed placebo (maltodextrin), a resveratrol-rich grape supplement (resveratrol 8 mg), or a conventional grape supplement lacking resveratrol, for the first 6 months and a double dose for the next 6 months.	1-year consumption of a resveratrol-rich grape supplement improved the inflammatory and fibrinolytic status in patients who were on statins for primary prevention of CVD and at high CVD risk (i.e., with diabetes or hypercholesterolemia plus ≥1 other CVD risk factor).The results showed for the first time that a dietary intervention with grape resveratrol could complement the gold standard therapy in the primary prevention of CVD.	(25)
To assess the effects of resveratrol, at the concentrations attainable after moderate wine intake, on platelet NO production and the mechanism of this activity.	Healthy Subjects (n=20) (Male-14; Feamle-6) Age=40-50yrs	Twenty healthy volunteers were studied before and after 15 days of controlled white or red wine intake (300 mL/d).	Intake of resveratrol in the form of moderate wine intake, activates platelet endothelial Nitric Oxide synthase (eNOS) and in this way blunts the proinflammatory pathway linked to P38 mitogen-activated protein kinase (p38MAPK), thus inhibiting Reactive oxygen species (ROS) production and ultimately platelet function. This activity contributes to the beneficial effects of oderate wine intake on ischemic cardiovascular disease.	(26)
To assess whether red wine has an effect on top of a lipid-lowering lifestyle in patients with carotid atherosclerosis.	Patients with carotid atherosclerosis. (n=108) (Male-72; Female-36) Age=37-83yrs	A randomised unblinded trial was performed from 2009 to 2011 in patients with carotid atherosclerosis, 65% of whom were already on statin therapy with a low mean LDL of 104.9 mg/dl. Half of them were advised to follow a modified Mediterranean diet and to perform moderate physical exercise during 30 min/day (lifestyle changes) for 20 weeks. Within these two groups half of the patients were randomised either to avoid any alcohol or to drink 100 ml of red wine (women) or 200 ml of red wine (men) daily.	Lifestyle changes including a modified Mediterranean diet and physical exercise as well as a glass of red wine daily improve independently the LDL/HDL ratio in patients with carotid arteriosclerosis even though the vast majority of them was already on statin therapy.	(27)

To examine the effects of moderate red wine intake on echocardio -graphic parameters of functional cardiac outcome in addition to inflammatory cytokines and nitrotyrosine (oxidative stress marker), in subjects with diabetes after a first uncomplicated Myocardial Infarction (MI).	Diabetic Subjects who sustained first non-fatal MI (n=115)	Subjects received a moderate daily amount of red wine (intervention group) or not (control group). Echocardiographic parameters of ventricular dys-synchrony, circulating levels of nitrotyrosine, tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), interleukin-18 (IL-18) and C-reactive protein (CRP) were investigated at baseline and 12 months after randomization.	In subjects with diabetes, red wine consumption, taken with meals, significantly reduces oxidative stress and pro-inflammatory cytokines as well as improving cardiac function after MI. Moderate red wine intake with meals may have a beneficial effect in the prevention ofcardiovascular complications after MI in subjects with diabetes.	(28)
To assess whether the lipid-lowering properties and antioxidants of the grape seed can be beneficial in atheroscler - osis prevention.	Mildly Hyperlipidemic subjects.(n=52)	The subjects were divided into two groups that received either 200 mg/day of the red grape seed extract (RGSE) or placebo for 8 weeks. After an 8-week washout period, the groups were crossed over for another 8 weeks. Lipid profiles and Ox-LDL were measured at the beginning and the end of each phase.	RGSE consumption reduced total cholesterol, LDL cholesterol, and Ox-LDL. While TG's and VLDL cholesterol were decreased and HDL cholesterol was increased by RGSE. RGSE consumption decreases Ox-LDL and has beneficial effects on lipid profile-consequently decreasing the risk of atherosclerosis and cardiovascular disorders-in mild hyperlipidemic individuals.	(29)
To examine the effect of wine intake on blood parameters (lipid, anti-oxidant capacity, and erythrocyte membrane potential and fluidity) in post myocardial infarct (MI) patients to evaluate perspectives in secondary prevention.	Selected Post Myocardial Infarct patients.	A clinical intervention trial was undertaken for 2 weeks. The study was conducted on hospitalized patients during a cardiac readaptation period. During which patients were submitted to a "Western prudent" diet (inspired by the Mediterranean diet) and two groups have been compared on a drawn basis: patients receiving red wine (250 mL daily) to patients receiving water. Physical, clinical, and blood parameters were evaluated on Days 1 and 14.	A positive effect of low wine consumption on blood parameters was seen that is (decrease in total cholesterol and LDL; increase in erythrocyte membrane fluidity and antioxidant status). These results show that moderate consumption of red wine even for a short period associated with a "Western prudent" diet improves various blood parameters in lipid and anti-oxidative status in patients with previous coronary ischemic accidents.	(30)
To elucidate whether the chronic consumption of red wine polyphenols improves risk factors associated with CVD in hypercholesterolaemic postmenopausal women.	Hypercholesterolaemic postmenopausal women (n=45)	Subjects were randomly assigned to consume 400 mL/day of either water, dealcoholised red wine (DRW) or full-complement red wine RW for 6 weeks following a 4-week washout. Fasting measures of lipids, lipoproteins, insulin and glucose were taken at 0 and 6 weeks.	DRW consumption had no effect of fasting concentrations of lipids, lipoproteins, insulin and glucose. However, chronic consumption of RW significantly reduced fasting LDL cholesterol concentrations by 8% and increased HDL cholesterol concentrations by 17% in hypercholesterolaemic postmenopausal women.Thus regular consumption of full-complement red wine reduces CVD risk by improving fasting lipid levels in hypercholesterolaemic postmenopausal women.	(31)
To investigate the relationship of wine consumption to Cardi-ovascular risk markers participating in SWAN (The study of women's health across the nation) over 7 years with repeated assessments of CV risk factors.	Multi-ethnic healthy subjects (n = 2900) (Women-2900) Age=42-52yrs	Subjects underwent annual exams which included interviews, anthropometry, questionnaires, and a blood draw for the assessment of all factors of interest including, reproductive hormones and CV risk factors. Outcome variables were CRP, factor VII activity, fibrinogen, PAI-1, and tPA measured in plasma. Wine consumption was assessed in all years. Total alcohol consumption was classified as none (<1/month),moderate (>1/month,≤1/week), and high (>1/week), providing a time-varying covariate	Moderate wine consumers had significantly lower levels of C-reactive protein, fibrinogen, factor VII and plasminogen activator inhibitor (PAI-1) than women who drank no or little wine. These associations were independent of significant effects of healthy lifestyle and overall alcohol consumption and similar across ethnic groups. Thus Moderate wine consumption may protect against CVD via inflammatory and clotting pathways.	(32)
To determine the in vivo effects of moderate red wine consumption on antioxidant status and oxidative stress in the circulation.	Healthy young and old subjects. (n=40) Young group(18-30yrs) = 20 subjects & Old group (50yrs and above) =20 subjects.	Each age group was randomly divided into treatment subjects who consumed 400 mL/day of red wine for two weeks, or control subjects who abstained from alcohol for two weeks, after which they crossed over into the other group. Blood samples were collected before and after red wine consumption and were used for analysis of whole blood glutathione (GSH), plasma malondialdehyde (MDA) and serum total antioxidant status.	Consumption of red wine induced significant increases in plasma total antioxidant status and significant decreases in plasma MDA and GSH in young and old subjects. The results show that the consumption of 400 mL/day of red wine for two weeks, significantly increases antioxidant status and decreases oxidative stress in the circulation.Thus red wine provides general oxidative protection and to lipid systems in circulation via the increase in antioxidant status and helps in preventing CVD.	(33)

To analyze the effect on LPS (plasma lipopolysaccharides) concentrations of chronic RW (Red wine) consumption and acute RW (Red wine) intake in relation to high fat intake in middle-aged men.	Middle-aged male volunteers. (n-10) (Male-10) Age=45-50yrs	Volunteers were randomly assigned in a crossover trial, and after a washout period, all subjects received RW, dealcoholized red wine (DRW), or gin for 20 d. Serum endotoxin and LPS-binding protein (LBP) concentrations were determined after the washout period and after each of the treatments, and changes in fecal microbiota were quantified. For the acute study, 5 adult men underwent a fat overload or a fat overload together with the consumption of RW, DRW, or gin. Baseline and postprandial serum LPS and LBP concentrations and postprandial chylomicron LPS concentrations were measured.	Chronic RW consumption increases Bifidobacterium and Prevotella amounts, which may have beneficial effects by leading to lower LPS concentrations,thus reducing the risk to CVD.	(34)

Moderate red wine consumption (one to two drinks per day; 10–30 g alcohol) in most populations, clinical advice to abstainers to initiate daily alcohol consumption has not yet been substantiated in the literature and must be considered with caution on an individual basis (20).

NOTE (Possible anti-atherogenic mechanisms of resveratrol. ↑Increase, ↓ Decrease, ApoB, Apolipoprotein-B; CETP, Cholesterol ester transport protein; COX, Cyclo-oxygenase; FC, Free cholesterol; FFA, Free fatty acids; HDL, High density lipoprotein; IL, Interleukin; LDL, Low density lipoprotein ;Lpn(a), Lipoprotein-A; LPG, Lipid peroxodation; PGE, Prostaglandin-E; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; TC, Total cholesterol; TG, Triglyceride; TNF-a, Tumour necrosis factor alpha; VCAM, vascular cell adhesion molecule; VLDL, Very low density lipoprotein.)

Fig.3 shows that natural and dietary antioxidants in the form of resveratrol intake have a vital role in preventing various diseases caused by oxidative stress including Artherosclerosis.

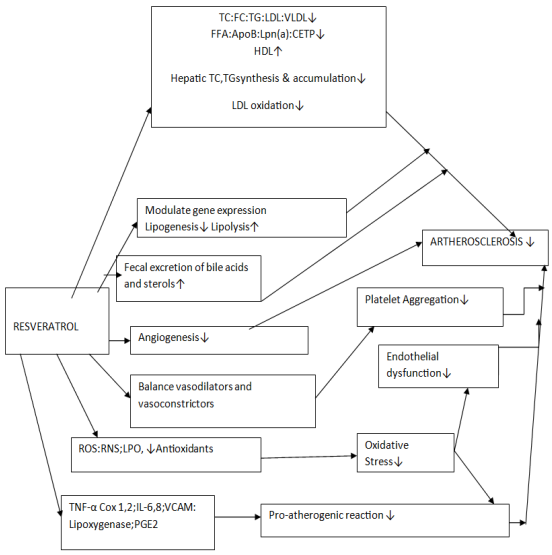

Fig 3 Mechanism of The Protective Effect of Resveratrol Against Atheriosclerosis

Oxidative stress impacts CVD risk, including atherosclerosis, through halting the production of free radicals and the oxidation process of LDL. Reactive oxygen species (ROS) leads to production and accumulation of oxidized LDL at the site of atherosclerotic lesions. Oxidative stress also progressively leads to the development of atherosclerosis by contributing to the formation of macrophage foam cells and causing endothelial dysfunction. RS is a strong anti-oxidant and helps by scavenging hydroxyl and superoxide radicals and by protecting the cells by preventing lipid peroxidation in the cell membranes as well as DNA damage. RS has been shown to prevent lipid peroxidation and inhibit uptake of oxidized LDL. This inhibition of lipid peroxidation by RS could arise from RS strong anti-oxidant effect and its ability to inhibit ROS generation.

Oxidation of LDL cholesterol is strongly associated with risk of CVD. RS could effectively prevent oxidative LDL modification by inhibiting lipoxygenase enzyme activity. Polyphenols in red wine including RS have been reported to inhibit LDL oxidation; this effect was found to be stronger than the well-known anti-oxidant a-tocopherol.RS also prevents the oxidation of polyunsaturated fatty acids found in LDL and inhibits the oxidized LDL uptake in the vascular wall in a concentration-dependent manner as well as prevents damage caused to lipids through peroxidation. Endothelial cells are known to regulate and maintain a balance between vasodilators such as nitric oxide and vasoconstrictors such as endothelin-1 reduce the risk of atherosclerosis by preventing atherogenesis. RS has been reported to influence and maintain a balance between production of vasodilators and vasoconstrictors respectively. RS inhibits the enzyme cyclooxygenase-1, which is a strong vasoconstrictor and has an important role in platelet aggregation. RS has been shown to increase the expression of nitric oxide synthase and hence, potentially protect perfused working hearts. The anti-oxidative properties of RS were suggested as the mechanism underlying its diverse effects including anti-atherogenic effects (21).

CONCLUSION

The emerging data from human clinical trials confirms what the past decade of in vitro and laboratory animal models have suggested; resveratrol has considerable potential to improve health and prevent chronic disease in humans. According to the research studies mentioned in this paper resveratrol intake helps in the prevention of various diseases like obesity, cancer, COPD, diabetes and CVD. In case of obesity about 150-1000mg/day of resveratrol has proven to be beneficial. A daily dose of resveratrol in the form of a resveratrol supplement or transresveratrol between 5mg-1g/day helps in the prevention of cancer and resveratrol in the form of grape polyphenol which is about 2g/day helps to protect against insulin ressistance. Whereas in case of CVD resveratrol in various forms like Resveratrol capsule ie 10mg/day, Resveratrol enriched grape extract ie 350mg/day, Resveratrol-rich grape supplement ie 8mg/day, Red grape seed extract ie 200mg/day or red wine consumption between 150-400ml/day

for around 3-6months protects against Cardiovascular diseases and its complications. However various doses of resveratrol supplement are prescribed depending on the disease condition and the degree to which it has affected the body. Thus resveratrol intake in moderation on a regular basis helps and is beneficial in metabolic, cardiovascular, mitochondrial and neurological disorders.

References

1. Das Dipak and Maulik Nilanjana (2006). Resveratrol in cardioprotection: a therapeutic promise of alternative medicine. Mol Interv; 6: 36–47.
2. Sun Weimin, Wang Wei, Kim Jung, Keng Peter, Yang Shanmin, Zhang Hengshan, Liu Chaomei, Okunieff Paul and Zhang Lurong(2008). Anti-cancer effect of resveratrol is associated with induction of apoptosis via a mitochondrial pathway alignment. Adv Exp Med Biol; 614:179–186.
3. Udenigwe Chibuike C, Ramprasath Vanu R, Aluko Rotimi E and Jones Peter JH (2008). Potential of resveratrol in anticancer and anti-inflammatory therapy. Nutr Rev; 66: 445–454.
4. Khurana Sandhya, Venkataraman Krishnan, Hollingsworth Amanda, Piche Mathew and T. C. Tai. (2013) Polyphenols: Benefits to the Cardiovascular System in Health and in Aging Nutrient; 5: 3779-3827.
5. Mukhopadhyay Partha, Pal Pacher and Das Dipak K 2(2011). MicroRNA signatures of resveratrol in ischemic heart Ann N Y Acad Sci; 1215: 109–116.
6. Timmers Silvie, Konings Ellen, Bilet Lena , Houtkooper Riekelt H. , Weijer Tineke van de, Goossens Gijs H. ,Hoeks Joris, Krieken Sophie van der, Dongryeol Ryu, Sander Kersten, Moonen-Kornips Esther, Hesselink Matthijs K.C., Kunz Iris, Schrauwen-Hinderling Vera B., Blaak,[b] Johan Auwerx, and Schrauwen Patrick (2011). Calorie restriction-like effects of 30 days of Resveratrol Ellen (resVida™) supplementation on energy metabolism and metabolic profile in obese humans.The Journal of Cell Metab. ; 14(5):612-22.
7. Robertson Paul R (2014). Red Wine and Diabetes Health: Getting Skin in the Game. The Pacific North west Diabetes Research Institute; 63(1):31-38.
8. Higdon Jane, Drake Victoria J and Steward William P (May 2008). "Resveratrol". Micronutrient Information Center. Linus Pauling Institute, Oregon State University.
9. Markus Andrea M and Morris Brian J (2008). Resveratrol in prevention and treatment of common clinical conditions of aging. Clin Interv Aging; 3(2): 331–339.
10. Witte Veronica A., Kerti Lucia, Daniel S. Margulies and Agnes Floel (2014). Effects of Resveratrol on Memory Performance, Hippocampal Functional Connectivity, and Glucose Metabolism in Healthy Older Adults. The Journal of Neuroscience; 34(23): 7862–7870
11. Dash Satya, Xiao Changting, Morgantini Cecilia, Szeto Linda and Lewis Gary F.(2013). High-Dose Resveratrol Treatment for 2 Weeks Inhibits Intestinal and Hepatic Lipoprotein Production in Overweight /Obese Men. The Arterioscler Thromb Vasc Biol.; 33:2895-2901.
12. Timmers Silvie, Konings Ellen, Bilet Lena, Houtkooper Riekelt H., Weijer Tineke van de, Goossens Gijs H., Hoeks Joris, Krieken Sophie van der, Dongryeol Ryu, Sander Kersten, Moonen-Kornips Esther, Hesselink Matthijs K.C., Kunz Iris, Schrauwen-Hinderling Vera B., Blaak,[b] Johan Auwerx, and Schrauwen Patrick (2011). Calorie restriction-like effects of 30 days of Resveratrol Ellen (resVida™) supplementation on energy metabolism and metabolic profile in obese humans.The Journal of Cell Metab. ; 14(5):612-22.
13. Zhu Weizhu, Qin Wenyi, Zhang Ke, Rottinghaus George E., Chen Yin-Chieh, Kliethermes Beth, Sauter Edward R.(2012). Trans-resveratrol alters mammary promoter hypermethylation in women at increased risk for breast cancer. Nutr Cancer.; 64(3):393-400.
14. Patel Ketan R. , Brown Victoria A., JL Jones Donald JL, Britton Robert G., Hemingway David, Miller Andrew S., West Kevin P. , Booth Tristan D. , Perloff Marjorie, Crowell James A., Brenner Dean E. , Steward William P., Gescher Andreas J., and Brown Karen(2010). Clinical Pharmacology of Resveratrol and its Metabolites in Colorectal Cancer Patients .The Journal of Cancer Res.; 70(19): 7392–7399.
15. Culpitt SV, Rogers DF, Fenwick PS, Shah P, Matos C.De, Russell R.E.K, Barnes PJ and Donnelly LE (2003). Inhibition by red wine extract, resveratrol, of cytokine release by alveolar macrophages in COPD. Thorax; 58:942–946.
16. Hokayem Marie, Blond Emilie, Vidal Hubert, Lambert Karen, Meugnier Emmanuelle, Coudray Christene Feillet, Coudray Charles, Pesenti Sandra, Luyton Cedric, Porcheron Stephanie Lambert, Sauvinet Valerie, Fedou Christine, Brun Jean-Frederic , Rieusset Jennifer, Bisbal Catherine, Sultan Ariane, Mercier Jacques, Goudable Joelle, Dupuy Anne-Marie, Cristol Jean-Paul, Laville Martine and Avignon Antoine (2013). Grape Polyphenols Prevent FructoseInduced Oxidative Stress and Insulin Resistance in First-Degree Relatives of Type 2 Diabetic Patients. Diabetes Care; 36:1454–1461.
17. Global status report on noncommunicable diseases 2010. Geneva, World Health Organization, 2011.
18. Global atlas on cardiovascular disease prevention and control. Geneva, World Health Organization, 2011.
19. Mathers Colin D and Loncar Dejon (2006). Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med; 3(11):e442
20. Giuseppe Lippi, Massimo Franchini, Favaloro Emmanuel J and Giovanni Targher (2010). Moderate Red Wine Consumptionand Cardiovascular Disease Risk: Beyond the French Paradox. Seminars in thrombosis and hemostasis; 36(1):59-70.
21. Ramprasath V R and Jones P J H (2010) Anti-atherogenic effects of resveratrol. *European Journal of Clinical Nutrition*; 64:660–668.
22. Magyar K, Halmosi R, Palfi A, Feher G, Czopf L, Fulop A, Battyany I, Sumegi B, Toth K and Szabados E(2012). Cardioprotection by resveratrol: A human clinical trial in patients with

stable coronary artery disease. Clin Hemorheol Microcirc.; 50(3):179-87.

23. Tomé-Carneiro J, Gonzálvez M, Larrosa M, García-Almagro FJ, Avilés-Plaza F, Parra S, Yáñez-Gascón MJ, Ruiz-Ros JA, García-Conesa MT, Tomás-Barberán FA and Espín JC(2012). Consumption of a grape extract supplement containing resveratrol decreases oxidized LDL andApoB in patients undergoing primary prevention of cardiovascular disease: a triple-blind, 6-month follow-up, placebo-controlled, randomized trial. *Journal of Molecular Nutrition & Food Research*; 56(5):810-21.
24. Tomé-Carneiro J, Gonzálvez Manuel, Larrosa Mar, Yáñez-Gascón Maria J, García-Almagro Francisco J, Jose A, Ruiz-Ros, Francisco A, Tomás-Barberán, García-Conesa and Espín Juan Carlos(2013). Grape resveratrol increases serum adiponectin and downregulates inflammatory genes in peripheral blood mononuclear cells: a triple-blind, placebo-controlled, one-year clinical trial in patients with stable coronary artery disease.*Journal of Cardiovascular Drugs And Therapy*; 27(1): 37–48.
25. Tomé-Carneiro J, Gonzálvez Manuel, Larrosa Mar, Yáñez-Gascón Maria J, García-Almagro Francisco J, Jose A, Ruiz-Ros, Francisco A, Tomás-Barberán, García-Conesa and Espín Juan Carlos (2012). One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. *The American Journal Of Cardiology*; 110(3):356-63.
26. Gresele Paolo, Pignatelli Pasquale, Guglielmini Giuseppe, Carnevale Roberto, Mezzasoma Anna Maria, Ghiselli Andrea, Momi Stefania and Violi Francesco (2008). Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production. *The Journal of Nutrition*; 138(9):1602-8.
27. Dirk W Droste, Iliescu Catalina, Vaillant Michel, Gantenbein Manon, Bremaeker Nancy De, Lieunard Charlotte, Velez Telma, Meyer Michele, Guth Tessy, Kuemmerle Andrea, Gilson Georges, and Chioti Anna(2013). A daily glass of red wine associated with lifestyle changes independently improves blood lipids in patients with carotid arteriosclerosis: results from a randomized controlled trial. *The Nutrition Journal*; 12(1):147.
28. Marfella R, Cacciapuoti F, Siniscalchi M, Sasso FC, Marchese F, Cinone F, Musacchio E, Marfella MA, Ruggiero L, Chiorazzo G, Liberti D, Chiorazzo G,Nicoletti GF, Saron C, D'Andrea F, Ammendola C, Verza M and Coppola L(2006). Effect of moderate red wine intake on cardiac prognosis after recent acute myocardial infarction of subjects with Type 2 diabetes mellitus. Journal Of Diabetic Medicine; 23(9): 974-81.
29. Razavi SM, Gholamin S, Eskandari A, Mohsenian N, Ghorbanihaghjo A, Delazar A, Rashtchizadeh N, Keshtkar-Jahromi M and Argani H(2013). Red grape seed extract improves lipid profiles and decreases oxidized low-density lipoprotein in patients with mild hyperlipidemia. *The Journal Of Medicinal Food*;16(3):255-8.
30. Rifler JP, Lorcerie F, Durand P, Delmas D, Ragot K, Limagne E, Mazué F, Riedinger JM, d'Athis P, Hudelot B, Prost M, Lizard G, Latruffe N(2012). A moderate red wine intake improves blood lipid parameters and erythrocytes membrane fluidity in post myocardial infarct patients. *Journal of Molecular Nutrition and Food Research*, 2012 Feb;56 (2):345-51.
31. Naissides Mary, John C.L. Mamo, Anthony P. James, Pal Sebely (2006). The effect of chronic consumption of red wine on cardiovascular disease risk factors in postmenopausal women. *The Journal of Atherosclerosis Research*.;185 (2): 438–445.
32. Janssen Imke, Landay Alan L., Ruppert Kristine and Powell Lynda H.(2014). Moderate wine consumption is associated with lower hemostatic and inflammatory risk factors over 8 years: The study of women's health across the nation (SWAN). Nutr Aging (Amst); 2(2-3): 91–99.
33. Micallef Micallef, Lexis Louise and Lewandowski Paul (2007). Red wine consumption increases antioxidant status and decreases oxidative stress in the circulation of both young and old humans. Nutrition Journal; 6:27.
34. Postigo Mercedes Clemente, Queipo-Ortun˜o Maria Isabel, Boto-Ordon˜ez Maria, Aragu¨ez Letica Coin, Rodriguez Maria del Mar Roca, Javier Delgado-Lista, Cardona Fernando, Lacueva Cristina Andres, and Francisco J Tinahones(2013). Effect of acute and chronic red wine consumption on lipopolysaccharide concentrations. Am J Clin Nutr; 97:1053–61.

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