# Resveratrol, Wine, and Atherosclerosis

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## Abstract

This review emphasizes the effects of resveratrol on factors involved in the mechanism of atherosclerosis and risk factors for atherosclerosis. The effects of wine and resveratrol on atherosclerosis are also discussed. Resveratrol is a potent antioxidant and an anti-inflammatory agent. It reduces the expression of cell adhesion molecules, monocyte colony stimulating factors, matrix metalloproteinases, and growth factors; and inhibits platelet aggregation and vascular smooth muscle cell proliferation. It reduces the serum levels of total cholesterol, triglycerides (TG), and raises high-density lipoprotein cholesterol, inhibits expression of C-reactive protein and lowers the levels of advanced glycation end products and its receptor in the vascular tissue. It lowers the risk factors for plaque rupture. Epidemiological data show that moderate consumption of alcohol has an inverse association with carotid atherosclerosis while high consumption has a positive association with carotid atherosclerosis. Wine reduces the extent of atherosclerosis in animal model. The antiatherosclerotic effect of wine is mainly due to it resveratrol content. Resveratrol reduces the extent of atherosclerosis in animal model of atherosclerosis (apolipoprotein [Apo] E-deficient and Apo $E^{-/-}$/low-density lipoprotein receptor-deficient mice and macrophage). In rabbit model of atherosclerosis, both reduction and acceleration of atherosclerosis have been reported with resveratrol. There are no data for regression and slowing of progression of atherosclerosis. Robust clinical trials for suppression of atherosclerosis are lacking. In conclusion, resveratrol has potential but experimental studies in depth and robust clinical trials are lacking for this agent to be of any value in the primary and secondary prevention of coronary and peripheral artery disease.

**Keywords**

- resveratrol
- atherosclerosis
- serum lipids
- inflammatory mediators
- C-reactive protein
- wine
- growth factors
- vascular smooth muscle cell proliferation
- matrix metalloproteinase

Heart disease and stroke are two of the three leading causes of death in Canada.[1] World Health Organization estimates that heart disease and stroke kill ~17 million/year globally and the fatalities are projected to increase to over 24 million/year by 2030. The number of deaths from myocardial infarction (MI) in United States is over 1 million/year.[2]

Atherosclerosis is the primary cause of ischemic heart disease and acute coronary syndrome, which comprises unstable angina, ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI). The proximal cause of acute coronary syndrome is thrombosis and the principal underlying cause is atherosclerosis. Plaque rupture and thrombosis are major causes of (90%) of MI.[3] Plaque rupture is because of weakening of the atherosclerotic plaque[4,5] as a result of overexpression of matrix metalloproteinases (MMPs).[6] Hyperlipidemia,[7–9] oxidative stress,[9–13] inflammation,[14–16] C-reactive protein (CRP),[17,18] advanced glycation end products (AGEs), and receptor for AGEs (RAGEs) axis[19–21] have been implicated in the development and progression of atherosclerosis. Mechanism of atherosclerosis involves oxidized low-density lipoprotein (OX-LDL), adhesion molecules, monocyte chemoattractant



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protein-1 (MCP-1), monocyte colony stimulating factor (MCSF), and macrophage-derived growth factor.[14,22]

Epidemiological data have shown that a prolonged and moderate consumption of red wine by the southern French and other Mediterranean populations is associated with low incidence of coronary heart disease (CHD) despite of a high-fat diet, little exercise, and heavy smoking (so-called French paradox).[23] Resveratrol is the active ingredient in wine and grapes. Among the possible mechanisms responsible for low incidence of CHD in these populations could be that resveratrol may have beneficial effects on the risk factors for atherosclerosis and the mechanism of initiation and progression of atherosclerosis. It is not known if the protective effect of wine is due to its alcohol or resveratrol content. Epidemiological data suggest a lower risk of cardiovascular disease[24,25] and cardiovascular mortality with moderate alcohol consumption.[26] Mukamal et al have reported that there is an inverse association between consumption of one to six drinks per week and carotid artery atherosclerosis.[27] These authors have also reported a positive association between consumption of more than 14 drinks/week and carotid artery atherosclerosis. Kiechl et al[28] have reported that carotid artery atherosclerosis is lowest in moderate drinkers and highest in heavy drinkers. Kuhanen et al[29] have reported that greatest progression of carotid artery atherosclerosis is in heavy drinkers. On the other hand, Demirovic et al[30] have reported that there is no association between alcohol consumption and carotid artery atherosclerosis.

This review will include resveratrol and its sources, wine and resveratrol, effects of resveratrol on the mechanisms of initiation and progression of atherosclerosis, risk factors for atherosclerosis, and plaque stabilization. The roles of resveratrol in atherosclerosis and its consequences will be also evaluated.

## Resveratrol and Its Source

Resveratrol is a natural, polyphenolic compound present in grapes, peanuts, and other plants and food products.[31,32] It is a fat-soluble compound occurring in two forms: trans and cis.[33] Trans-resveratrol has been studied in detail.[34] Pharmacological activity of cis-resveratrol is much less known. Concentrations of resveratrol in some natural foods are shown in ►**Table 1**.

**Table 1** Resveratrol Content in Certain Natural Foods[33–37]

| | |
|---|---|
| Grapes | 0.16–3.54 μg/g |
| Dry grape skin | ~24.06 μg/g |
| Red grape juice | ~0.5 mg/L |
| White grape juice | ~0.05 mg/L |
| Red wine | 0.1–14.5 mg/L |
| White wine | 0.1–2.1 mg/L |
| Peanuts | 0.02–1.92 μg/g |
| Pistachios | 0.09–1.67 μg/g |

## Wine and Resveratol

A concentration of resveratrol in wine varies. Red wines contain between 0.2 and 5.8 mg/L depending upon the grape variety, while white wine contains ~0.68 mg/L.[33,38] Red wine is extracted with skin intact whereas white wine is fermented after removal of skin. Red wines have six times more trans-resveratrol than white wines while white wines have high concentrations of cis-resveratrol.[39]

## Mechanism of Atherosclerosis

The mechanism of atherosclerosis involves oxidation of low-density lipoprotein cholesterol (LDL-C) and accumulation in macrophages leading to foam cell formation.[14,22] Low-density lipoprotein (LDL) is mildly oxidized to minimally modified low-density lipoprotein (MMLDL), which stimulates smooth muscle cells and endothelial cells to produce MCP-1. Adherence of monocyte to the endothelial cells involves expression of various adhesion molecules (endothelial leukocyte adhesion molecules [ELAMs], vascular cell adhesion molecules-1 [VCAM-1], intercellular adhesion molecules-1 [ICAM-1], and soluble intercellular adhesion molecule-1 [sICAM-1]) on the endothelial cells.

MMLDL is further oxidized to OX-LDL. MCP-1 and OX-LDL are involved in migration of monocyte to subendothelial area. Monocytes express receptor for LDL, but the rate of uptake of native LDL is insufficient to produce foam cells. Monocyte/macrophage differentiation is facilitated by release of MCSF from endothelial cells with the help of MMLDL. Differentiated macrophage develops receptors for OX-LDL which is taken up to form foam cells. Genes expressed in these cells determine the replication of macrophage, smooth muscle cells replication and migration, T-cell replication, and chemotaxis of additional monocytes. Macrophages generate numerous growth-regulating molecules (platelet-derived growth factor [PDGF], basic fibroblast growth factor [bFGF], transforming growth factor-β [TGF-β]) and cytokines.[40,41] Gene expression and transcription in smooth muscle cells results in the formation of collagen, elastic fiber proteins, and growth regulating molecules (bFGF and insulin-like growth factor-1 [IGF-1]).[42] Endothelial cells produce growth-promoting molecules (PDGF, bFGF, TGF-β, IGF-1). MCSF helps in stability and replication of macrophages.[43,44] Both PDGF and IGF-1 are chemoattractant for smooth muscle cells. bFGF and MCSF are chemoattractant for endothelial cells and for macrophages, respectively. TGF-β stimulates synthesis of connective tissue and matrix including collagens, proteoglycans, and elastic fiber protein.[45] The mechanisms outlined above lead to smooth muscle cell proliferation and migration, synthesis of connective tissue and matrix, migration of monocytes, and formation of lipid-laden macrophage, resulting in the development and progression of atherosclerosis.

## Effects of Resveratrol on Mechanism Involved in Atherosclerosis

From the above discussion on the mechanism of atherosclerosis it appears that there are numerous players including

endothelial cells, monocytes, oxygen radicals, adhesion molecules, MCP-1, MCSF, foam cells, smooth muscle cells, the growth factors (PDGF, bFGF, TGF-β, IGF-1), and cytokines in the genesis and maintenance of atherosclerosis. To be effective in suppression, slowing of progression, and regression of atherosclerosis, a drug should have inhibitory effects on the numerous players stated above. In this section, the assessment is being made of the possible effects of resveratrol on the key factors involved in the genesis and maintenance of atherosclerosis.

## Antioxidant Activity of Resveratrol

Oxidation of LDL is an early and critical event in the genesis of atherosclerosis. Reduction in the levels of reactive oxygen species (ROS) would suppress, regress, and slow the progression of atherosclerosis. Resveratrol has effects on the production and metabolism of ROS. Resveratrol reduces ROS production in cardiac tissue of guinea pig.[46] It inhibits the production of intracellular and extracellular ROS[47] and reduces hydrogen peroxide ($H_2O_2$) production by OX-LDL.[48] Resveratrol increases the activities of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) and levels of glutathione, an ROS scavenger in rat aortic smooth muscle cell.[49,50] It increases the catalase activity in cardiac tissue of guinea pigs.[46] It increases endogenous antioxidants[51] and scavenges peroxyl, hydroxyl, and superoxide anion radicals.[47,52,53]

Resveratrol prevents/reduces oxidation of LDL in high fat-fed rats.[49,54,55] It inhibits lipid peroxidation.[56,57] Heme oxygenase-1 (HO-1) degrades pro-oxidant heme to biliverdin/bilirubin, iron, and carbon monoxide. Bilirubin scavenges free radicals. Resveratrol increases the expression of HO-1 in aortic smooth muscle cells[58] and hence would reduce the ROS levels. Resveratrol also inhibits the activity of enzymes which are involved in production of ROS. It inhibits nicotinamide adenine dinucleotide phosphate-oxidase,[59] hypoxanthine/xanthine oxidase,[60] and myeloperoxidase.[61] The antioxidant activity of resveratrol is summarized in ►**Table 2**.

The above data suggest that resveratrol is a potent antioxidant because it inhibits production, accelerates activity of enzymes that metabolizes ROS, decreases the activity of enzyme that plays a role in production of ROS and scavenges ROS.

**Table 2** Antioxidant Activity of Resveratrol[49,50,58–61]

| Increased Activity | Decreased Activity |
|---|---|
| • SOD<br>• Catalase<br>• GSH-Px<br>• Glutathione reductase<br>• Glutathione-S-transferase<br>• HO-1 | • NADPH oxidase<br>• Hypoxanthine/xanthine oxidase<br>• Myeloperoxidase |

SOD, superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase.

## Resveratrol and Inflammatory Mediators

Inflammation plays a role in the genesis of atherosclerosis.[62] Proinflammatory cytokines increase expression of chemokines and adhesion molecules.[62,63] Resveratrol inhibits the activity of inflammatory enzymes—cyclooxygenase and lipoxygenase.[64,65] It inhibits the production of interleukin (IL)-1,[66] IL-2, IL-12, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α),[67–69] IL-6,[70] IL-4,[71] and IL-8.[72] It attenuates proinflammatory transcription factor, nuclear factor-kappa B (NF-kB), and activator protein-1.[73] IL-18 is a proatherogenic and proinflammatory cytokine that enhances the inflammatory cascade by inducing the expression of proinflammatory cytokines, chemokines, and adhesion molecules that have been implicated in atherosclerosis. Venkatesan et al[74] have reported that resveratrol attenuates IL-18.

MCP-1 recruits monocyte to the site of inflammation and induces atherosclerosis. Resveratrol inhibits the TNF-α-induced MCP-1 secretion and gene transcription.[75] Resveratrol inhibits MCP-1-induced monocytes migration.[76] The data suggest that resveratrol attenuates the production of proinflammatory cytokines and hence would be effective in suppression, regression, and slowing of progression of atherosclerosis.

## Resveratrol and Cell Adhesion Molecules

Cell adhesion molecules are involved in the adherence of monocyte to the endothelial surface which is the initial step in the migration of monocyte to subendothelial area. Resveratrol decreases the expression of ELAM and VCAM-1.[77,78] It suppresses expression of ICAM-1 and VCAM-1,[79,80] and E-selectin[81] on endothelial cells. Ferrero et al[82] have reported that resveratrol reduces granulocyte and monocyte adhesion to endothelial cells.

## Resveratrol and Macrophages

As stated in the section "Mechanism of Atherosclerosis," MCSF helps in maturation of monocyte to macrophage which then develops receptors for uptake of OX-LDL resulting in foam cell formation. Inhibition of expression of MCSF and formation of foam cells would be effective in reducing the development of atherosclerosis. Resveratrol significantly inhibits MCSF and granulocyte colony stimulating factor.[83] Park et al[84] have reported that resveratrol inhibits the foam cell formation induced by lipopolysaccharides by reducing ROS generation and MCP-1 expression.

## Resveratrol and Growth Factor

As outlined in the section on mechanism of atherosclerosis, growth factors such as PDGF, bFGF, TGF-β, and IGF-1 play important role in the development of atherosclerosis. In this section the author discusses if resveratrol has any effect on the growth factors. Resveratrol has a potent antiproliferative activity on vascular smooth muscle cell (VSMC).[85,86] This effect could be due to inhibition of PDGF-receptor mitogenic signaling. It has been reported that resveratrol inhibits PDGF-receptor mitogenic signaling in mesangial cells.[87] Trans-resveratrol inhibits PDGF-stimulated DNA synthesis and cell proliferation in cultured VSMC.[88] Pterostilbene, a natural

demethylated analog of resveratrol significantly inhibits DNA synthesis and proliferation of PDGF-stimulated VSMCs.[89]

Vascular endothelial growth factor (VEGF) and bFGF stimulate endothelial migration, proliferation, and tubule formation during angiogenesis in keeping with the progression of atherosclerosis. Resveratrol could suppress atherosclerosis by inhibiting VEGF- and bFGF-induced angiogenesis. Resveratrol directly affects the human umbilical vein endothelial cells by inhibiting VEGF-induced tubule formation.[90] Uchiyam et al[91] have reported that resveratrol inhibits VEGF- and bFGF-induced angiogenesis in a mouse vascular endothelial cell line. It has been reported that resveratrol inhibits multiple myeloma angiogenesis by inhibiting expression and secretion of VEGF and bFGF.[92] Resveratrol has potent antiproliferative affect through reduction in TGF-β content.[93] It downregulates TGF-$\beta_2$.[94] It suppresses IGF-1.[95]

### Resveratrol and VSMC Proliferation

VSMC proliferation plays an important role in development and progression of atherosclerosis, as their proliferation and migration contribute to intimal thickening. Resveratrol inhibits proliferation of VSMCs.[85,86] The antiproliferative effect of resveratrol is mediated by G1-S block in cell cycle but not by induction of apoptosis.[96,97] Resveratrol in lower concentration suppresses VSMC proliferation not by apoptosis, but in higher concentration it induces apoptosis.[86] It inhibits AGE-induced VSMC proliferation.[98]

### Resveratrol and Platelet Aggregation

Platelet aggregations have been implicated in the genesis of atherosclerosis. The mechanisms involved include generation of ROS by activated platelet. Resveratrol inhibits human platelet aggregation in vitro.[99,100] However, resveratrol had little effect on platelet in whole blood.[101] Wang et al[102] have reported that in vitro resveratrol inhibited platelet aggregation induced by collagen, thrombin, and adenosine diphosphate in a concentration-dependent manner. They also reported that resveratrol inhibited platelet aggregation in vivo.

### Resveratrol and MMPs

Dysregulation of extracellular matrix metabolism from local overexpression of MMPs [6] may weaken atherosclerotic plaque, causing their rupture.[3–5] Active MMPs contribute to matrix degradation, remodelling and weakening of atherosclerotic lesions, and rupture of vulnerable plaques. Plaque rupture and thromboembolism cause the majority (~90%) of MIs.[3] MMP-2 and MMP-9 have been implicated in VSMC migration leading to intimal thickening and atherosclerotic lesions. Expression of MMP-9 has been implicated in the progression of atherosclerosis.[103,104] It has also been reported that MMP is critical for atherogenesis because of its ability to regulate both proliferation and migration of smooth muscle cells.[105,106] From the foregoing data it appears that MMP-2 and MMP-9 are not only involved in the atherogenesis but also in the instability of atherosclerotic plaques. Resveratrol inhibits the expression of MMP-2 and MMP-9 in fibrosarcoma cell[107] and TNF-α-induced MMP-9 expression in human VSMCs.[108]

## Effects of Resveratol on Risk Factors for Atherosclerosis

There are numerous risk factors for development of atherosclerosis, including dyslipidemia, diabetes, hypertension, cigarette smoking, obesity, chromic infection, CRP, homocysteine, and AGEs and its receptors (RAGE).[14,20] However, this section will deal only few risk factors such as dyslipidemia, CRP, AGEs-RAGE axis where the effects of resveratrol have been investigated.

### Serum Lipid

The effects of resveratrol on serum lipids are conflicting. However, most of the studies show a decrease in total cholesterol (TC), LDL-C, and increase in high-density lipoprotein cholesterol (HDL-C). Dietary resveratrol dose-dependently reduces the serum TG, LDL-C, and very low-density lipoprotein cholesterol (VLDL-C) in hepatoma-bearing rats.[109] It decreased the serum levels of TC, LDL-C, and TG but increased the levels of serum HDL-C and HDL-C/TC ratio in high-cholesterol diet-induced hyperlipidemic rats.[110] It reduced plasma levels of TG, free cholesterol (FC) in Syrian golden hamsters on high-cholesterol diet but had no effect on HDL-C.[111] Cho et al[111] also reported that resveratrol significantly reduced apolipoprotein (Apo)-B and lipoprotein(a) but elevated the serum levels of Apo-A-1 and Apo-A-1/Apo-B ratio and that the reduction of serum TC was due to down-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase mRNA expression. Do et al[112] have reported that resveratrol reduced serum levels of TC, LDL-C, and activity of HMG-CoA reductase and elevated the serum levels of HDL-C and HDL-C/TC ratio in Apo E-deficient (Apo $E^{-/-}$) mice. However, resveratrol administered in the dose of 20 mg/kg body weight for 14 days to rats on high cholesterol diet reduced LDL-C and TG.[113] Rocha et al[49] have reported decreases in the serum TC and LDL-C with resveratrol (1 mg/kg body weight in drinking water) in rats on high fat diet. Decreases in the serum TC, LDL-C, and VLDL-C with resveratrol have also been reported in hepatoma-bearing rat.[109] Nihei et al[114] have reported that resveratrol in the dose of 50 mg/kg body weight daily for 14 days substantially reduced hyperlipidemia and hepatic synthesis of lipids. Decreases in serum TC and FC with resveratrol in the dose of 0.0125% in diet have also been reported.[115] In a long-term study, it has been reported that resveratrol in the dose of 10 mg/kg for 8 weeks in obese Zueker rats reduced plasma TG and TC.[116] Studies have also shown that resveratrol has no effects on serum lipids. Turrens et al[117] have reported that trans-resveratrol had no effect on serum lipoprotein profile in normal rats. It is possible that resveratrol does not have hypolipidemic effect and the effect is only when the serum levels of lipids are elevated. However, resveratrol had no hypolipidemic effects in experimentally induced hypercholesterolemia in rabbits.[118] There are other studies which

show that resveratrol had no effect on serum lipids in hyperlipidemic rabbits.[32,102]

### Resveratrol and Serum CRP

CRP is an acute phase protein, synthesized and secreted primarily in hepatocytes[119] and regulated by IL-1, IL-6, and TNF-α.[120] CRP is not only an important and unique risk marker, but also has an important role in the pathogenesis of inflammation and atherosclerosis.[121–123] The studies suggest that CRP is proatherogenic and promotes atherosclerosis.[124,125] CRP levels are increased in patients with acute coronary syndrome and predict in-hospital and short-term adverse outcomes[126,127] and have been implicated in the pathophysiology of restenosis following percutaneous coronary interventions.[128,129]

As CRP plays a role in atherogenesis, lowering of CRP would be beneficial in preventing/reducing the development of atherosclerosis. Epidemiological data suggest that moderate consumption of alcohol especially red wine, reduces mortality from coronary artery disease (CAD).[25] It has been reported that resveratrol in the concentration of 50 μM reduced cytokine-induced CRP expression.[130] Kaur et al[130] also reported that resveratrol in the concentration of 25 to 50 μM produced 50% inhibition of CRP. Sicilian red wine consumption reduces plasma CRP.[131]

### Resveratrol and Ages and RAGE Axis

AGEs and receptors for AGEs (RAGE, soluble RAGE [sRAGE]) axis has been implicated in the development of atherosclerosis.[132–135] Interaction of AGEs with full length RAGE leads to increase expression of adhesion molecules and cytokines,[136–138] activation of NF-kB,[137] which in turn increases the expression of proinflammatory genes for adhesion molecules and cytokines[136] and generation of oxygen radicals.[139,140] These agents are involved in the development of atherosclerosis as has been discussed in an earlier section of this review (see the section on Effects of Resveratrol on Mechanisms Involved in Atherosclerosis). sRAGE circulates in the blood[141] and acts as decoy for RAGE ligands and competes with RAGE for ligand binding,[142] thus preventing the activation of full-length RAGE. Reduction in RAGE and serum AGE and increasing the serum levels of sRAGE may reduce the development of atherosclerosis.

Resveratrol reduces the expression of RAGE in the VSMCs.[143] Also it prevents the impairment of AGE on macrophage-lipid homeostasis partially by suppressing RAGE via peroxisome proliferator-activated receptor gamma activation.[144] Resveratrol has been shown to reduce AGE levels in chondrocytes isolated from pig joint.[145]

## Resveratol and Atherosclerosis

All the attributes of resveratrol discussed in the previous sections indicate that resveratrol would have beneficial effect on atherosclerosis. It has a potential for becoming an antiatherogenic agent. To be of potential benefits in patients with atherosclerosis, a drug should also regress or/and slow progression of atherosclerosis. In this section, the effects of wine and resveratrol on suppression, regression, and slowing of progression of atherosclerosis will be discussed.

### Wine and Atherosclerosis

The effects of wine on atherosclerotic changes are summarized in ►**Table 3**. The data on epidemiological studies on the effects of wine and protection of cardiovascular disease have been inconsistent. Wine drinkers are at a lower risk of cardiovascular disease than beer or liquor drinker.[146–148] Moderate alcohol consumption has been consistently associated with 20 to 30% reductions in CHD. Consumption of one to six drinks per week of alcohol had inverse association with carotid atherosclerosis and consumption of 14 or more drinks has a positive association with carotid atherosclerosis.[27] Carotid atherosclerosis is lowest in moderate drinkers and highest in heavy drinkers.[28] However, it has also been

**Table 3** Effects of Wine on Suppression of Atherosclerosis

| Human and Animal Species | Dose | Atherosclerotic Changes |
|---|---|---|
| Human | • Moderate drinkers<br>• 1–6 drinks of alcohol/wk<br>• 14 or more drinks of alcohol/wk<br>• Moderate drinkers<br>• Heavy drinkers | 20–30% reduction in CAD[146–148]<br>Inverse association with CA[27]<br>Positive association with CA[27]<br>Lowest CA[28]<br>Highest CA[28] |
| Apo $E^{-/-}$ mice | Red wine containing 1.1% alcohol (0.5 mL/mice/d) | ↓ 48%[149] |
| Rabbits | • Resveratrol (3 mg/kg/d)<br>• Red wine (4 mL/kg/d) containing 3.98 mg resveratrol/L<br>• De-alcoholized red wine (4 mL/kg/d) containing 3.23 mg resveratrol/L<br>• Red wine<br>• Red wine and nonalcoholic red wine | ↓[154]<br>↓[154]<br>↓[154]<br>↓[151]<br>↓ Similar extent[152] |
| Hamsters | • 6.75% alcohol<br>• Red wine with 6.75% alcohol<br>• Red wine without alcohol<br>• Grape juice without vitamin C | ↓ 18.3%[155]<br>↓ 52.9%[155]<br>↓ 45.2%[155]<br>↓ 27.6%[155] |

wk, week; CAD, coronary artery disease; CA, carotid atherosclerosis; Apo $E^{-/-}$ mice, apolipoprotein E-deficient mice; d, day; ↓, decrease.

reported that there is no association between alcohol consumption and carotid atherosclerosis.[30] It is not clear, however, whether red wine phenols confer additional protection.

There are some studies on the effect of wine on the atherosclerotic lesion in the animal model. Red wine containing 1.1% alcohol in the dose of 0.5 mL/mice daily for 6 weeks reduced the development of atherosclerosis in Apo $E^{-/-}$ mice by 48%.[149] Alcohol-free red wine has been reported to reduce atherosclerosis in Apo $E^{-/-}$ mice.[150]

In rabbit model of atherosclerosis, the effects of wine are contradictory. Klurfeld and Kritchevsky[151] have shown that only red wine, among alcoholic beverages such as beer, white wine, and whisky, was more effective than ethanol alone in reducing extent of atherosclerosis in rabbits. In other study, it has been reported that red wine and a nonalcoholic red wine concentrate reduced atherosclerotic lesion to the same extent in rabbit.[152] However, contrary to above, red wine or alcohol consumption for 3 months had no effect on atherosclerosis in rabbit.[153] The effects of wine could be due to alcohol content. Wang et al[154] investigated to determine if resveratrol has alcohol-independent effects on atherosclerosis in rabbits. They compared the effects of de-alcoholized Chinese red wine with that of Chinese red wine with comparable amounts of resveratrol on the atherosclerotic changes in high cholesterol-fed rabbits. The rabbits were given resveratrol (3 mg/kg/d) or red wine (4 mL/kg/d) containing 3.98 mg/L resveratrol or de-alcoholized red wine (4 mL/kg/d) containing 3.23 mg/L resveratrol for 12 weeks. They showed that the size, density, and mean area of atherosclerotic plaques and thickness of intima were significantly reduced in rabbits on high cholesterol diet given de-alcoholized red wine, red wine, or resveratrol compared with rabbits on high cholesterol diet alone. The reductions in atherosclerosis were similar with de-alcoholized red wine and resveratrol. The data suggested that resveratrol, and not alcohol, has antiatherosclerotic effect of wine.

Vinson et al[155] investigated the effects of red wine with or without alcohol on the atherosclerotic changes in aorta of hamster on high cholesterol diet to determine if active ingredient in red wine is responsible for beneficial effect of wine. They showed that 6.75% alcohol, red wine with 6.75% alcohol, red wine without alcohol, and grape juice without vitamin C suppressed the development of atherosclerosis by 18.3, 52.9, 45.2, and 27.6%, respectively. These effects were associated with reduction in serum lipids and oxidative stress. These data suggest that all ingredients of wine are effective in reducing atherosclerosis in this model and the maximum effect resides in nonalcoholic ingredients in wine.

### Resveratrol and Atherosclerosis

The effects of resveratrol on atherosclerotic changes are summarized in ►**Table 4**. The effects of resveratrol on atherosclerotic lesion in various animal model (Apo $E^{-/-}$ and Apo $E^{-/-}$/low-density lipoprotein receptor [LDLR]$^{-/-}$ mice, rabbits) and in vitro have been reported. Resveratrol in the doses of 0.02 and 0.06% w/w in the semisynthetic diet for 20 weeks reduced the atherosclerotic changes in Apo $E^{-/-}$ mice and this effect was associated with decreases in plasma TC, LDL-C, and TG, hepatic HMG-CoA reductase, ICAM-1, and VCAM-1 in atherosclerotic lesion, and increases in serum HDL-C, HDL-C/TC ratio, and Apo-A1/Apo-B ratio.[156] Trans-resveratrol in the dose of 9.6 mg and 96 mg/kg diet for 8 weeks in mice lacking both Apo E and LDLR (Apo $E^{-/-}$/$LDLR^{-/-}$) on high fat diet reduced the atherosclerotic lesion by 30% without any change in TC and TG.[157]

Castro et al[158] reported that resveratrol (3 mg/kg/d) given for 60 days to high cholesterol-fed rabbits reduced the high cholesterol-diet-induced atherosclerotic change in the subendothelial tunica of intima and tunica media. However, in one study Wilson et al[159] reported that resveratrol in the dose of 0.6 mg/kg/d for first 5 days, and then 1.0 mg/kg/d for an additional 55 days given to rabbits on high cholesterol diet accelerated atherosclerosis by 63% (high cholesterol vs. high cholesterol + resveratrol; 40.81 ± 24.63% vs. 66.87 ± 18.92%).

In vitro THP-1 monocyte/macrophages model of atherosclerosis, THP-1 monocyte/macrophages were incubated with or without resveratrol (50 μM) for 24 hours. Resveratrol reduced the foam cell formation in THP-1 macrophages with or without IFN-γ.[160]

## Comments

Resveratrol has many pharmacological effects including suppression of factors involved in the mechanism of genesis of atherosclerosis and reduction in risk factors for atherosclerosis. It is an antioxidant and anti-inflammatory agent, reduces

**Table 4** Effects of Resveratrol on Suppression of Atherosclerosis

| Animal Species | Dose | Atherosclerotic Changes |
|---|---|---|
| Apo $E^{-/-}$ mice | 0.02 and 0.06% w/w in diet | ↓[156] |
| Apo $E^{-/-}$/$LDLR^{-/-}$ mice | 9.6 mg and 96 mg/kg diet | ↓ 30%[157] |
| Rabbits | 3 mg/kg body weight/d | ↓[158] |
| | 0.6 mg/kg body weight/d for 5 d and then 1 mg/kg body weight/d for 55 d | ↑ 63%[158] |
| Macrophage model of atherosclerosis (in vitro) | 55 μM | ↓ Foam cell formation[160] |

Apo $E^{-/-}$ mice, apolipoprotein E-deficient mice; $LDLR^{-/-}$ mice, low-density lipoprotein receptor-deficient mice; d, day; ↓, decrease; ↑, increase.

expression of cell adhesion molecules, MCSF, MMPs, and growth factors (PDGF, bFGF, TGF-β, IGF-1, and VEGF); and inhibits platelet aggregation and VSMCs proliferation. In general, it reduces the serum TG, TC, and raises HDL-C, inhibits expression of CRP and lowers levels of AGE and RAGE. It reduces the risk factors (MMPs and cytokines) for plaque ruptures. Resveratrol appears to have all the attributes for suppression of atherosclerosis. However, the effect of resveratrol on atherosclerosis varies. In general, it suppresses atherosclerosis in Apo $E^{-/-}$ and Apo $E^{-/-}$/$LDLR^{-/-}$ mice and hamsters, but the effects of rabbit are variable (from suppression to acceleration). These differences could be due to the differences in the animal model and the doses used. It has a potential for being a novel agent from dietary sources in suppression, regression, and slowing of progression of coronary artery atherosclerosis, hence reducing the incidence of CAD and its consequences. Robust studies on suppression of atherosclerosis with resveratrol are lacking. The studies on regression and slowing of progression of atherosclerosis in animal model are lacking. Case–controlled randomized clinical trials for suppression, regression, and slowing of progression of atherosclerosis are required to establish the efficacy of resveratrol in coronary artery and peripheral vascular diseases. Experimental data for suppression of atherosclerosis are available, but clinical trials for its efficacy in primary and secondary prevention of CAD and its consequences are lacking.

## Conclusion

Resveratrol has all the attributes to suppress, regress, and slow progression of atherosclerosis. It suppresses experimental atherosclerosis but its effects on regression and slowing of progression of atherosclerosis are not known. Antiatherosclerotic effect of red wine is mainly due to its resveratrol content. There are no robust clinical trials for suppression, regression, and slowing of progression of atherosclerosis. Resveratrol has potential but experimental studies in depth and clinical trials are lacking to be of any value in the primary and secondary prevention of coronary and peripheral arterial diseases.

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