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The effects of wine consumption on cardiovascular disease and associated risk factors: a narrative review

Pierre-Louis Teissedre[1, 2*], Creina Stockley[3], Mladen Boban[4], Philippe Gambert[5], Marta Ortiz Alba[6], Markus Flesh[7] and Jean-Claude Ruf[8]

[1] Université de Bordeaux, Institut des Sciences de la Vigne et du Vin, EA 4577, Unité de recherche Œnologie, 210 chemin de Leysotte, CS 50008, F-33882 Villenave d'Ornon Cedex, France
[2] INRA, ISVV, USC 1366 Œnologie, F-33882 Villenave d'Ornon, France
[3] The Australian Wine Research Institute, PO Box 197, Glen Osmond, SA, 5064, Australia
[4] Department of Pharmacology - University of Split, School of Medicine, Soltanska 2, 21 000 Split, Croatia
[5] IFR 100 Santé STIC, Laboratoire de Biochimie Médicale, Plateau Technique de Biologie, 2 rue Angélique Ducoudray, BP 37013, 21070 Dijon Cedex, France
[6] Universidad Nacional de Cuyo - Facultad de Ciencias Médicas, Química Biológica, Avenida Libertador 80, 5500 Mendoza, Argentina
[7] Allgemeine Innere Medizin / Kardiologie, Marienkrankenhaus Soest, Widumgasse 5, 59494 Soest, Germany
[8] International Organisation of Vine and Wine (OIV), Scientific coordinator, 18 rue d'Aguesseau, 75008 Paris, France

The authors are government delegates and/or experts to the International Organisation of Vine and Wine's (OIV) Commission IV Safety and Health. Although this work was initiated under the auspices of the OIV and its Consumption, Nutrition and Health expert group, the statements made herein are solely the responsibility of the authors.

Abstract

Accumulating evidence suggests that regular moderate consumption of wine can positively influence risk factors associated with cardiovascular health. These effects are often attributed to grape and wine-derived phenolic compounds and their effects on risk factors such as atherosclerosis, for which mechanisms have been clearly identified, such as a decrease in the oxidation of LDL-cholesterol and reduction of oxidative stress, and an increase in nitric oxide and related restoration of endothelial function. In addition, the ethanol component of wine increases HDL-cholesterol, inhibits platelet aggregation, promotes fibrinolysis and reduces systemic inflammation.
Scientific research needs to be conducted, however, before we can begin to provide science-based dietary recommendations, although there is sufficient evidence to generally recommend consuming food sources rich in bioactive compounds such as wine in moderation.
This narrative review examines published evidence on the cardioprotective effects associated with wine-derived compounds, with a primary focus on the development and progression of atherosclerosis and thrombosis.

Keywords: wine, cardiovascular diseases, consumption, polyphenols, ethanol, pathophysiological mechanisms

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*Corresponding author : pierre-louis.teissedre@u-bordeaux.fr

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Cardiovascular events are the primary cause of mortality and morbidity in both developed and developing countries, accounting for approximately 20% of all deaths. Clinical cardiovascular events are mainly of atherothrombotic origin. "Atherothrombosis" associates two fundamental conditions. Atherosclerosis is where lesions affect the vessel wall of arteries, reducing their medium diameter. Reactive thrombosis occurs on these advanced lesions especially when they rupture. Without thrombotic reactivity, even the most advanced arterial lesion would remain clinically silent. Atherosclerotic lesions are triggered by a genetic background associating numerous metabolic dysfunctions, such as hypercholesterolemia, hyperhomocysteinemia, hyperglycemia and hypertension, together with environmental factors. Thrombotic reactivity depends also on the genetic background and some predisposing conditions, such as hypercoagulability and hyperviscosity. Recently, Stockley (2012) examined the suggestions and evidence surrounding the relationship between light-to-moderate alcohol consumption and human health benefits. Numerous epidemiological studies have demonstrated an inverse correlation between moderate consumption of alcohol and the incidence of coronary artery disease (CAD) and myocardial infarction, in comparison to an increased risk in lifelong abstainers (Kannel 1988; Moore *et al.*, 1990; Shaper *et al.*, 1988). The inclusion of "sick quitters" in the control group in some studies published prior to 2007 had prompted some research groups to suggest that this unduly influenced estimates of the extent of alcohol's cardioprotection (Fillmore *et al.*, 2007).

In contrast, the large Norwegian Nord-Trøndelag Health (HUNT) study was undertaken in a population characterized by low average alcohol consumption, where abstinence is not socially stigmatized (Gémes *et al.*, 2016a, b). Frequent, light-to-moderate alcohol consumption appeared most cardioprotective and this relationship was not driven by the misclassification of former drinkers. Specifically, there was an inverse correlation between alcohol consumption and risk of CAD and myocardial infarction, as well as heart failure, where frequency of alcohol consumption was more strongly associated with risk than overall quantity consumed. A dose response meta-analysis of 18 prospective studies totalling 214,340 participants and 7,756 CAD cases suggested, however, that the optimum amount of alcohol to reduce risk is 36 g/day (Yang *et al.*, 2016). A subsequent population-based cohort study by Bell *et al.* (2017) extended the inverse correlation between alcohol consumption and risk to other common cardiovascular diseases including angina, ischaemic stroke, peripheral arterial disease, and abdominal aortic aneurysm, and to all-cause mortality. Compared with moderate alcohol consumers (32 g/day for men and 24 g/day for women), abstainers had a 32% increased risk of fatal cardiovascular disease and a 24% increased risk of all-cause mortality and, similarly, heavy alcohol consumers.

Beneficial effects of moderate consumption of alcoholic beverages on cardiovascular diseases

The vast majority of epidemiological studies consistently show that moderate consumption of alcoholic beverages is associated with a reduced incidence of mortality from different cardiovascular diseases by 20 to 50% compared to lifelong abstainers (Boffetta and Garfinkel, 1990; Camargo *et al.*, 1997a; Doll *et al.*, 1994; Marmot and Brunner 1991). This is particularly true for those individuals with one or more risk factors for cardiovascular diseases such as hypertension, cigarette smoking, hypercholesterolemia, obesity and diabetes (Camargo *et al.*, 1997b; de Gaetano *et al.*, 2016; di Castelnuovo *et al.*, 2017; Gronbaek *et al.*, 1994). However, it is still in dispute whether any one of the three types of alcoholic beverages ─ wine, beer or spirits ─ is more cardioprotective than the others (di Castelnuovo *et al.*, 2009; Perissinotto *et al.*, 2010). A review by Rimm *et al.* (1996) concluded that all alcoholic beverages were associated with lower risk, and the beneficial effects on coronary heart disease (CHD) could be attributed to the common alcohol component itself. However, a meta-analysis by de Gaetano *et al.* (2016) confirmed the J-shaped association between wine consumption and vascular risk and provided evidence for a similar relationship for beer. In a meta-analysis of 10 studies on spirit consumption and vascular risk, no J-shaped relationship could be found (Costanzo *et al.*, 2011).

Most of these investigations were based on populations consuming one predominant type of alcoholic beverage, which precluded valid comparison of the effects of the three different types of alcoholic beverages. Earlier epidemiological and clinical studies of alcoholic beverages suggested that wine consumption might confer additional benefits (Renaud and de Lorgeril, 1992; Renaud *et al.*, 1999; Rotondo and de Gaetano 2000) and several more recent studies have also been published giving individual relative risks attributable to the consumption of wine, beer or spirits. Many of these have shown that wine drinkers had a lower risk for death from CHD than did non-wine drinkers at all levels of total alcohol consumption (di Castelnuovo *et al.*, 2002; Farchi *et al.*, 1992; Friedman and Kimball,

1986; Gronbaek *et al.*, 1995; Gronbaek *et al.*, 2000; Klatsky, 2003; Klatsky *et al.*, 1990; Renaud *et al.*, 1998).

Animal and human clinical studies have, however, suggested that the polyphenols found in abundance in fruits and tea, as well as in wine, may reduce the risk of death from CHD by delaying the development if its precursor atherosclerosis.

Animal studies supporting a protective effect of wine against athero-thrombosis

Much experimental evidence supports a protective role of dietary phenolic compounds against cardiovascular diseases such as atherosclerosis (Arts and Hollman, 2005), and it is widely hypothesized that they protect against atherosclerosis by preventing one or more of the processes involved in disease progression, such as oxidative stress, inflammation, and endothelial dysfunction.

Atherosclerosis progresses when macrophages in the sub-endothelial space of an artery take up oxidized low density lipoprotein (LDL) through a non-regulated scavenger receptor and are converted to foam cells which contain excessive lipids, especially cholesterol ester. The continuing aggregation of foam cells and cholesterol esters in the sub-endothelial space leads to the formation of fatty streaks, which are the earliest identifiable lesions of atherosclerosis (referred to as early atherosclerosis).

Polyphenols appear to exert both direct anti-oxidation effects, which include direct reactive oxygen species (ROS) scavenging activity and transient metal chelation, and indirect effects to prevent the development and progression of atherosclerosis (Mladěnka *et al.*, 2010). Three polyphenols in particular (+)-catechin, quercetin (Qer) and resveratrol (Res), have been shown to prevent *in vitro* and *in vivo* LDL free radical-mediated oxidation (Frankel *et al.*, 1993, Teissedre *et al.*, 1996). Several animal studies also suggested, however, that while red wine extract and catechin (Cat) did not prevent atherosclerotic lesions, a highly significant reduction of thrombotic reactivity was observed with administration of red wine and Cat (Bentzon *et al.*, 2001; Soulat *et al.*, 2006).

Auger *et al.* (2005) subsequently studied the effects of Cat, Qer and Res on early atherosclerosis in hamsters. Hamsters (n = 32) were divided into four groups of eight and fed an atherogenic diet for 12 weeks, also receiving once a day either tap water (control) or a solution of Cat, Qer or Res in water (total volume of 7.14 mL/kg body wt/day). The doses of phenolic compounds used were 2.856 mg of (+)-catechin/kg body wt/day, 0.1428 mg of quercetin/kg body wt/day, and 0.1428 mg of resveratrol/kg body wt/day, which mimics moderate consumption of alcohol-free red wine, approximately equivalent to that supplied by the consumption of about two glasses of red wine per meal for a 70 kg human adult. Plasma cholesterol concentration was lower in the groups that consumed the phenolic compounds than in the control group. The increase in plasma apolipoprotein (Apo) A1 concentration was mainly due to Cat (26%) and Qer (22%) and, to a lesser but not significant extent, Res (19%). ApoB was not affected. Plasma antioxidant capacity was not improved, and there was no sparing effect on plasma vitamins A and E. Plasma iron and copper concentrations were not modified, nor were liver super oxide dismutase and catalase activities. A sparing effect of Qer on liver glutathione peroxidase activity appeared, whereas Cat and Res exhibited a smaller effect. Aortic fatty streak area was significantly reduced in the groups receiving Cat (84%), Qer (80%) or Res (76%) in comparison with the control group. These findings demonstrated that Cat, Qer and Res at nutritional doses prevent the development of atherosclerosis through several indirect mechanisms.

Auclair *et al.* (2009) investigated the anti-atherosclerotic effects of Cat alone supplemented in the diet of ApoE deficient mice. After six weeks of supplementation, atherosclerotic lesions were assessed by histomorphometry and several markers of lipid, inflammation and oxidative stress status were evaluated. Cat supplementation reduced the mean atherosclerotic lesion area by 32% but had no effect on total cholesterol and triacylglycerol levels in plasma and liver. Also, markers such as the plasma antioxidant capacity (FRAP) and the inflammatory status (serum amyloid A) were unchanged. The expression of 450 genes, however, was significantly modified by Cat supplementation. Some of the most significantly down-regulated genes included those coding for adhesion molecules such as CD34 and PSGL-1, which are known to play a key role in leukocyte adhesion to the endothelium. Other genes involved in energy metabolism, lipid metabolism and lipid trafficking such as FABP4, LPL and SCARA5 were also down-regulated and may contribute to the atheroprotective effect of Cat.

Other potential indirect effects of polyphenols that in pharmacologically achievable concentrations may also be responsible for their positive cardiovascular influence include direct inhibition of some radical-forming enzymes (xanthine oxidase, NADPH

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oxidase and lipoxygenases), decreased platelet aggregation and leukocyte adhesion, and vasodilatory properties, each of which requires specific structural features. For example, a catecholic B-ring is necessary for scavenging activity; hydroxyl groups in an ortho position, the 3-hydroxy-4-keto group, or the 5-hydroxy-4-keto group enable iron chelation; planar conformation with the 4-keto group and 2,3-double bond is essential for inhibition of leukocyte adhesion and platelet aggregation; specific hydroxy-methoxy ortho conformation in ring B is necessary for the inhibition of NADPH oxidase; and the 4-keto group is a requisite for vasodilatory action.

Loke *et al.* (2010) investigated whether individual dietary polyphenols representing different classes of polyphenol compounds could inhibit the development of atherosclerosis and, specifically, reduce atherosclerotic lesion formation in the ApoE-/- gene-knockout mouse. The polyphenols investigated ─ Qer (flavonol) (-)-epicatechin (flavan-3-ol), theaflavin (dimeric catechin), sesamin (lignan), and chlorogenic acid (phenolic acid) ─ were incorporated into the diet and given at a dose corresponding to achievable human intake. Qer and theaflavin (64 mg/kg body mass/day) significantly attenuated atherosclerotic lesion size in the aortic sinus and thoracic aorta ($P<0.05$ versus ApoE-/- control mice). Qer significantly reduced aortic F2-isoprostane, vascular superoxide, vascular leukotriene B4, and plasma-sP-selectin concentrations, and increased vascular endothelial nitric oxide (NO) synthase activity, heme oxygenase-1 protein, and urinary nitrate excretion ($P<0.05$ versus ApoE-/- control mice). Theaflavin showed similar, although less extensive, significant effects. Although (-)-epicatechin significantly reduced F2-isoprostane, superoxide, and endothelin-1 production ($P<0.05$ versus ApoE-/- control mice), it had no significant effect on lesion size. Sesamin and chlorogenic acid treatments exerted no significant effects. Qer, but not (-)-epicatechin, significantly increased the expression of heme oxygenase-1 protein in lesions versus ApoE-/- controls. The data collectively suggested that dietary polyphenols, and particularly Qer and theaflavin, may attenuate atherosclerosis in ApoE-/- gene-knockout mice by inhibiting inflammation, improving NO bioavailability, and inducing heme oxygenase-1, which was subsequently confirmed by Shen *et al.* (2013). The data also suggested that inhibition of oxidative stress is generally neither sufficient, nor necessary, for polyphenols to inhibit atherosclerosis in ApoE-/- mice. It was concluded that the cardiovascular protection associated with diets rich in fruits, vegetables and certain beverages may, in part, be the result of flavonoids, such as Qer, through a combination of effects.

Although antioxidants, including phenolic compounds, prevented the development of atherosclerosis in animal models, the observation in human clinical intervention studies that antioxidants such as polyphenols are of no benefit to patients with established atherosclerosis (Steinberg and Witztum, 2002; Steinhubl, 2008; Willcox *et al.*, 2008) led researchers to question whether free radicals are actually involved or responsible for atherogenesis and CHD. Animal model studies have generally used young animals or initiated the intervention when introducing the high-fat or high-carbohydrate diets. Gendron *et al.* (2010) using a mouse model tested the hypothesis that during aging more severe dyslipidemia leads to the accumulation of endothelial damage that cannot be reversed by an antioxidant treatment. In short, prevention with antioxidants such as Cat is beneficial, whereas intervention is not. To this end, LDLr -/-; hApoB+/+ atherosclerotic (ATX, 9 months old) and pre-ATX (3 months old) male mice were treated with Cat (30 mg/kg/day) up to 12 months of age. At 12 months of age, vascular function and endothelium/leukocyte interactions were studied. Renal artery endothelium-dependent dilations were impaired with age, whereas adhesion of leukocytes onto the native aortic endothelium was increased ($P<0.05$). Aortic oxidative stress (ROS) increased ($P<0.05$) at 3 months in ATX and at 12 months in wild-type mice. Aorta mRNA expression of NADPH oxidase increased, whereas that of manganese superoxide dismutase decreased in 12-month-old ATX mice only. In mice with established ATX, Cat (from 9 to 12 months) reduced ($P<0.05$) by approximately 60% ROS without affecting plaque burden. Notably, Cat worsened endothelial dysfunction and further increased leukocyte adhesion ($P<0.05$) in ATX mice. In contrast, the same Cat treatment reversed all age-related dysfunctions in wild-type mice. On the other hand, in pre-ATX mice treated for 9 months with Cat, plaque burden was reduced by 64% ($P<0.05$) and all vascular markers were normalized to the 3-month-old values.

Consequently, it can be hypothesized that regular and moderate wine consumption reduces the incidence of ischaemic cardiovascular events, not primarily by effects on arterial lesions but by effects on thrombotic reactivity. In contrast, heavy wine consumption is an established risk factor for hypertension and the development and progression of atherosclerosis, and is associated with lower fibrinolytic activity, pro-coagulation events, and higher blood viscosity (Toth *et al.*, 2014). For example, alcohol-induced oxidative

stress/ROS production, accumulation of fatty acid ethyl esters, modification of lipoproteins, as well as increased expression of pro-inflammatory cytokines and vascular cellular adhesion molecules, all contribute to and promote the formation of atherosclerotic plaques (Hannuksela *et al.*, 2002). In addition, the alcohol-induced increase in blood pressure may counteract direct atheroprotective mechanisms.

Pathophysiological explanations

The cardioprotective effects of alcohol, substantially identical irrespective of the type of alcoholic beverage, can be distinguished from the effects of exclusive wine components, such as polyphenols. These different effects may in part explain the greater reduction in risk noted in many studies with wine when compared to other alcoholic beverages, and include serum lipid changes and anti-oxidation activity, effects on haemostasis and fibrinogen, anti-inflammation, endothelial or vascular function, and others described as follows.

1. Serum lipids

The most recognized and probably the most important mechanism to explain the role of alcohol in preventing CHD is the increased rate of high density lipoprotein (HDL), its different fractions (HDL2 and HDL3), and components (ApoA1 and ApoA2). Moreover, in all prospective studies that assessed the levels of HDL (or its fractions), HDL is negatively correlated with the risk of ischaemic heart disease. Conversely, heavy alcohol consumption elevates serum triglycerides, thereby potentially increasing vascular risk, most probably due to a genetic predisposition (de Oliveira e Silva *et al.*, 2000; Gaziano *et al.*, 1993; Nishiwaki *et al.*, 1994).

2. Anti-oxidation

The inverse relationship between dietary flavonoid consumption and cardiovascular diseases may be associated with the ability of wine polyphenols to attenuate LDL oxidation, macrophage foam cell formation and atherosclerosis (Frankel *et al.*, 1993; Teissedre *et al.*, 1996). The effect of wine polyphenols on arterial cell-mediated oxidation of LDL is determined by their accumulation in the lipoprotein and in arterial cells, such as macrophages. Wine polyphenols can reduce LDL lipid peroxidation by scavenging reactive oxygen/nitrogen species. Since wine seems to be more effective as antioxidant than other alcoholic beverages, many authors have sought to demonstrate that this was the result of the high content of antioxidant compounds in wine. Indeed, wine contains many compounds, including Qer, Cat and Res, all of which have antioxidant properties *in vitro* (Frankel *et al.*, 1993; Mikstacka *et al.*, 2010; Pinzani *et al.*, 2010; Sun *et al.*, 2009). Red, but not white wine, inhibits the oxidation of human LDL *in vitro*, presumably due to the difference in polyphenol content. Oxidation of the polyunsaturated lipid components of LDL with ROS may have a role in atherosclerosis.

Red wine is also able to prevent fat oxidation during digestion, which is a novel means to lower the damaging effects of these oxidized fats from, for example, beef meat, on the cardiovascular system (van Hecke *et al.*, 2016). Apparently, wine procyanidins are particularly active in preventing lipid oxidation of food while in the digestive tract, thus preventing the postprandial plasma rise in oxidants. The likely limited bioavailability of these compounds, therefore, does not affect their relevance as key elements for optimizing nutrition and reducing risk of atherogenesis (Covas *et al.*, 2010; Modun *et al.*, 2008; Tsang *et al.*, 2005). Indeed, many researchers consider the GI tract as the major site of action of nutritional antioxidants where they may act as chemical antioxidants. In that way, wine polyphenols may prevent the production and absorption of toxic products of lipid oxidation, thereby counteracting postprandial oxidative and associated damaging inflammatory responses (Gorelik *et al.*, 2008; Halliwell *et al.*, 2000; Ursini and Sevanian, 2002). In contrast to the GI tract, at systemic level in cells, basic kinetic considerations rule out scavenging of radicals as effective antioxidant defense. Instead, polyphenols may function through their metabolism in cells to electrophiles that induce antioxidant enzymes and elevate concentration of the nucleophiles, thereby improving cellular resilience to oxidative stress (Forman and Ursini, 2014; Forman *et al.*, 2014; Plauth *et al.*, 2016).

In addition, wine consumption is associated with moderate and transient elevation in plasma uric acid, the most abundant antioxidant in human plasma, which may significantly contribute to the postprandial antioxidative effects of wine (Modun *et al.*, 2008).

3. Haemostasis

Another explanation for the protective action of alcohol pertains to its effect on platelets, which play a critical role in thrombosis and the pathogenesis of atherosclerosis. Numerous studies have shown that alcohol inhibits platelet aggregation, a key step in

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haemostasis, in humans as well as in animals in response to several agonists, such as collagen, thrombin, adenosine diphosphate (ADP) and platelet activating factor (PAF). Studies that have investigated the effect of wine and wine polyphenols on platelet activation and aggregation have also shown a significant inhibitory effect on ADP and thrombin-induced platelet aggregation (Crescente *et al.*, 2009; Keevil *et al.*, 2000; Meade *et al.*, 1979; Renaud *et al.*, 1992). Using ADP and thrombin as agonists, Qer and Res both exhibit a dose-dependent inhibition of human platelet aggregation (Bertelli *et al.*, 1996; Pace-Asciak *et al.*, 1995). Another anti-thrombotic effect of wine and wine polyphenols is their capacity to prevent the potentially damaging rebound overshoot of platelet aggregation after withdrawal of alcohol, which partly explains the increase in sudden deaths and haemorrhagic strokes at the end of a weekend or holiday following a binge pattern of alcohol consumption beforehand (Ruf, 2004; Ruf *et al.*, 1995).

4. Fibrinogen

An increase in plasma fibrinogen is generally considered an independent risk factor for atherosclerosis and cardiovascular disease (Koenig *et al.*, 1998). Fibrinogen is, due to its size, shape and high plasma concentration, a major determinant of plasma viscosity. In a recent prospective epidemiological study, the consumption of alcoholic beverages, and particularly wine and spirits, was strongly associated with the concentration of fibrinogen in plasma. This association was J- or a U-shaped where plasma fibrinogen concentration was highest for both non-drinkers and those who drank more than 60 g/day of alcohol (de Curtis *et al.*, 2005; de Lange *et al.*, 2004; Estruch *et al.*, 2004; Hansen *et al.*, 2005, Imhof *et al.*, 2004, Karatzi *et al.*, 2004; Mezzano, 2004; Mezzano and Leighton, 2003).

5. Anti-inflammation

Activated platelets not only facilitate further platelet accumulation but may also recruit polymorphonuclear (PMN) and mononuclear leukocytes by expressing specific adhesive proteins like P-selectin, a receptor mediating platelet-leukocyte binding (Djurovic *et al.*, 2007; Sacanella *et al.*, 2007). There is growing evidence that wine polyphenols may have anti-inflammatory effects. The grape and wine component resveratrol inhibits adhesion molecule expression and monocyte adhesion *in vitro* (Naito *et al.*, 2004, Williams *et al.*, 2004). Studies provided information showing that wine polyphenols inhibit PMN and mononuclear leukocytes adhesion to stimulated platelets in a dose-dependent manner. This inhibition is due to the reduction by the wine polyphenols of the expression of adhesion molecule such as b2-integrin (MAC-1). More recently, it has been shown that gallic acid, an abundant red wine polyphenol, antagonizes P-selectin-mediated platelet-leukocyte interactions (Carluccio *et al.*, 2003; Estruch *et al.*, 2004; Ferrero *et al.*, 1998).

6. Vascular function

Endothelium-derived NO is an important regulator of vascular tone. Many studies have provided direct evidence that wine polyphenols induce an endothelial-dependent relaxation via a direct enhancement of endothelial NO synthesis (Brizic *et al.*, 2009; Chalopin *et al.*, 2010; de Gaetano *et al.*, 2002; Ndiaye *et al.*, 2005; Sarr *et al.*, 2006). In addition to its vasodilator properties, NO can convey vasoprotection in several ways. NO released toward the vascular lumen is a potent inhibitor of platelet aggregation and adhesion to the vascular wall. Besides protection from thrombosis, this also prevents the release of platelet-derived growth factors that stimulate smooth muscle proliferation and its production of matrix molecules. Endothelial NO also controls the expression of genes involved in atherogenesis. NO decreases the expression of the chemoattractant protein MCP-1, and of surface adhesion molecules such as CD11/CD18, P-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), thereby preventing leukocyte adhesion to vascular endothelium and leukocyte migration into the vascular wall (Duarte *et al.*, 2004; Novakovic *et al.*, 2006; Wang *et al.*, 2006). Considering the whole family of polyphenols and stilbenes compounds, it appears that resveratrol protects the cardiovascular system by mechanisms that include defense against ischaemic-reperfusion injury, promotion of vasorelaxation, protection and maintenance of intact endothelium, anti-atherosclerotic properties, inhibition of LDL oxidation, suppression of platelet aggregation, and estrogen-like actions.

7. Other effects

Plasma viscosity is influenced by diseases with altered plasma protein composition, and higher platelet membrane microviscosity is another risk factor for atherosclerosis and cardiovascular disease. Red wine polyphenols have an antioxidative effect on the polyunsaturated fatty acids in the platelet lipid membranes that makes them less reactive (Polette *et al.*, 1996), and red wine (but not white wine)

consumption has accordingly been shown to reduce platelet membrane microviscosity, where platelet membrane total saturated fatty acids decreased after red wine consumption whereas total unsaturated fatty acids (poly and mono) showed a tendency to increase after red wine consumption. These results may have a synergistic effect in decreasing platelet aggregation (Jensen *et al.*, 2006; Mansvelt *et al.*, 2002). The antioxidant properties of wine polyphenols are also involved in the anti-aggregatory effect. Certain flavonoids, such as catechin or epicatechin, for example, are able to increase and restore endogenous alpha-tocopherol levels or decrease malondialdehyde (MDA) formation, a marker for lipid peroxidation, in platelets co-incubated with docosahexaenoic acid (DHA), a long-chain polyunsaturated fatty acid observed to reduce platelet aggregation (Polette *et al.*, 1996). Flavonoids have specifically been shown to inhibit the non-enzymatic peroxidation of polyunsaturated fatty acids required for the activation of cyclo- and lipoxygenase. By reacting with the reactive compound of the radical, flavonoids stabilize ROS and because of the high reactivity of the hydroxyl group of the flavonoids, the radical is made inactive.

The adipokine adiponectin might represent an important link between insulin resistance, type 2 diabetes, and atherosclerosis. Adiponectin improves insulin sensitivity and has several anti-inflammatory properties (Aldhahi and Hamdy, 2003), where higher concentrations of adiponectin are associated with lower risk of type 2 diabetes (Duncan and Schmidt, 2006; Spranger *et al.*, 2003) and future cardiovascular events (Pischon *et al.*, 2004). Moderate consumption of alcoholic beverages is associated with increased adiponectin concentrations in healthy individuals, in obese males, and in women with impaired glucose tolerance and type 2 diabetes (Beulens *et al.*, 2006; Beulens *et al.*, 2007; Beulens *et al.*, 2008; Sierksma *et al.*, 2004). While the alcohol component common to all alcoholic beverages is associated with increased adiponectin concentrations, the impact of non-alcoholic ingredients such as polyphenols on adiponectin concentrations has been questioned. Experimental and clinical data suggest that sex hormones affect adiponectin concentrations. Among healthy males, the effects of alcohol consumption on sex hormones has been shown to vary by drinking pattern and between beer and wine consumption (Couwenbergs, 1988; Nishizawa *et al.*, 2002; Rinaldi *et al.*, 2006), such that the type of alcoholic beverage consumed and specifically its polyphenol content may differentially affect adiponectin concentrations. Moreover, in an animal model, the chronic consumption of grape-derived polyphenols was found to prevent diet-induced obesity by improving oxidative stress markers such as adipokine secretion (Décordé *et al.*, 2009).

Serum HDL-associated paraoxonase 1 (PON1) reduces oxidative stress in lipoproteins, macrophages and atherosclerotic lesions, whereas paraoxonase 2 (PON2), which is present in tissues but not in serum, acts as an antioxidant at the cellular level. Both PON1 and PON2 protect against the development of atherosclerosis, which may be related to their antioxidant properties. Supplementation with low doses of red wine polyphenols significantly reduced plasma homocysteine levels and restored the hepatic and plasma-decreased PON1 activity induced by chronic hyperhomocysteinemia. Moreover, quercetin and moderate alcohol consumption significantly inhibit the progression of atherosclerosis by up regulating the hepatic expression of the anti-atherogenic gene, PON1, with concomitant increased serum PON1 activity (Leckey *et al.*, 2010; Noll *et al.*, 2009; Rosenblat and Aviram, 2009).

Conclusions

Estruch and Lamuela-Raventos (2014) succinctly summarize the known biological mechanisms behind alcohol's observed cardioprotective effects. Discrepancies remain, however, regarding the specific effects of different types of beverages on the cardiovascular system, and also whether the possible protective effects of alcoholic beverages are due to their alcohol component (ethanol) or to non-alcoholic components, mainly polyphenols. Recent randomized clinical trials have shown that wine, a polyphenol-rich alcoholic beverage, potentially provides higher antioxidant and anti-inflammatory effects than some spirits such as gin, a polyphenol-free alcoholic beverage. Also, human clinical trials have shown that lower daily wine consumption by women delivers similar cardioprotective effects to men consuming higher amounts of alcohol.

The biological mechanisms of moderate and regular wine consumption that underlie the cardioprotective effects therefore need to be better understood. In particular, effort is needed to define wine consumption in physiologically relevant quantitative units, the dosage and pattern of consumption required to achieve physiologically relevant polyphenol concentrations in body fluids, and thereby to conduct *in vivo* studies at physiologically relevant concentrations. In addition, a comparison of wine consumption effects in relation to different diet types and lifestyles is required, as well as details of wine

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consumption in terms of alcohol content, phenolic content and structures, and origins.

Only scientific evidence accumulated from an unbiased selection of epidemiological, extensive animal, cell culture and human clinical studies will not promulgate misinformation. Indeed, all recent population studies show a significant and meaningful reduction in the risk of cardiovascular disease and total mortality from moderate consumption of alcoholic beverages such as wine. Epidemiologists who previously raised concerns of statistical bias have more recently concluded: "For drinkers having one to two drinks per drinking day without episodic heavy drinking, there is substantial and consistent evidence from epidemiological and short-term experimental studies for a beneficial association with ischaemic heart disease (IHD) risk when compared to lifetime abstainers. The alcohol-IHD relationship fulfills all criteria for a causal association proposed by Hill." (Roerecke and Rehm, 2014).

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