International Journal of Wine Research

Dovepress
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MINI-REVIEW

Red wine and cardiovascular health: the "French Paradox" revisited

This article was published in the following Dove Press journal:
International Journal of Wine Research
16 January 2010
Number of times this article has been viewed

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Abstract: The healthful and nutritive properties of wine have been acknowledged for thousands of years, but the observation that moderate consumption of red wine on a regular basis may be preventative against coronary disease is recent. Dr Renaud, a scientist working at the Bordeaux University in France, suggested wine consumption explains the "French Paradox", the low incidence of heart attacks in France regardless of a remarkable dietary intake of saturated fats and alcohol. After nearly 20 years of research, there is now mounting evidence that light to moderate wine intake is beneficial for the cardiovascular health, acting through a variety of mechanisms that target all the crucial steps of atherosclerosis, from early formation of the atherosclerotic plaque to its life-threatening complications (ulceration, thrombosis, vessel occlusion and infarction). These effects are attributable to the synergic properties of several biochemical components of wine (alcohol, resveratrol, and especially polyphenolic compounds), particularly the red varieties. This article reviews the leading clinical observations and the hypothesized biological mechanisms that strongly support the cardiovascular benefits of moderate red wine consumption on cardiovascular health and that would make red wine a promising therapeutic supplement to prevent and even perhaps treat coronary artery disease.

Keywords: wine, cardiovascular disease, coronary disease, atherosclerosis

Introduction

The healthful and nutritive properties of wine have been acknowledged for thousands of years, considering that Hippocrates recommended specific wines to purge fever, disinfect and dress wounds, as diuretics, or for nutritional supplements, around 450 BC. Moreover, the first official report synthesizing a number of evidences about the beneficial effect of polyphenolic compounds in red wine is dated back 1410 AD. Nevertheless, the first epidemiological observation that the French population suffers a relatively low incidence of coronary heart disease (CHD), despite a relatively high dietary intake of saturated fatty acids, was first described by the Irish physician Samuel Black in 1819, and later named the "French Paradox".[1] Dr Renaud, a scientist working at the Bordeaux University in France, suggested wine as an explanation for this paradoxical observation.[2] After re-evaluation of previously published studies, Renaud concluded that the protective effect of red wine appears to be essentially associated with tannins (polyphenols) extracted either from grape seeds or from wine itself.[3]

Clinical evidence

Moderate intake of alcohol from any type of alcoholic beverage has been strongly associated with several beneficial effects on the cardiovascular system. In 1979, St. Leger and

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colleagues first described a strong inverse relationship between wine consumption and risk of death from coronary disease in various countries.[4] Since then several epidemiological studies have further assessed the beneficial effects of regular wine consumption on the cardiovascular risk,[2,5–11] supporting a U- or J-shaped relationship between alcohol intake and mortality from all causes (the descending leg of the curve results from a decreased risk of cardiovascular disease among those with light-to-moderate alcohol consumption).[12]

Strong evidence of a pronounced beneficial effect of red wine on the cardiovascular health emerged from the Copenhagen City Heart Study in 1995. In this study, 13,285 men and women aged 30–70 years were followed-up for ~12 years. Remarkably, it was concluded that the risk of cardiovascular mortality steadily decreased with increasing intakes of red wine, from a relative risk (RR) of 1.00 for the subjects who never drank wine to 0.51 (95% confidence interval [95% CI]: 0.32–0.81) for those who drank three to five glasses per day.[13] For spirits intake, however, the RR of dying increased from 1.00 for those who never drank to 1.34 (95% CI: 1.05–1.71) for those with an intake of three to five drinks per day. A nonsignificant trend in mortality risk was also observed in relation to the subjects drinking beer compared with those who never drank beer.[13] Gronbaek and colleagues performed a further large epidemiological study, including 24,623 subjects over 10 years, and assessed the long-term effect of one to three glasses of alcoholic beverage (beer or wine) per day on cardiovascular mortality and concluded that subjects with low-to-moderate wine intake had nearly half the risk (RR 0.51; 95% CI: 0.32–0.81) of dying from cardiovascular causes compared with drinkers of beer, spirit and non drinkers.[9] These results were confirmed in a further systematic review of large population-based cohort studies by the same authors. Compared with nondrinkers, light-to-moderate drinkers had a RR of death from all causes of 0.90, whereas the addictive benefit of drinking conferred additional advantages, lowering the RR to 0.66.[8] Renaud and colleagues investigated 36,250 French middle-aged men, and found that moderate red wine consumption, but not other alcoholic beverages, reduced all-cause mortality over 18 years.[14] In a 20-year follow-up study of 128,934 adults in northern California, light-to-moderate drinkers were deemed to be at lower risk from cardiovascular mortality (RR for one to two drinks per day = 0.7; 95% CI: 0.6–0.9). A preferential intake of red wine was associated with a lower relative risk for coronary disease mortality compared with other alcoholic beverages, whereas the risk of noncardiovascular mortality was higher in heavy drinkers (≥6 drinks per day) than in nondrinkers (RR = 1.6; 95% CI: 1.3–2.0).[11] In a long-term epidemiological investigation, Thun and colleagues assessed the effect of alcohol consumption on mortality on 490,000 middle-aged and elderly US adults, who were followed for nine years. The cardiovascular mortality rates were 30% to 40% lower in men (RR, 0.7; 95% CI: 0.7–0.8) and women (RR, 0.6; 95% CI: 0.6–0.7) who reported at least one drink daily than those in nondrinkers. The all-cause mortality rate was also lower among men and women reporting approximately one drink daily.[15] More recently, Djoussè and colleagues[16] investigated the association between alcohol consumption and cardiovascular risk and death in 26,399 female participants from the Women's Health Study, observing a J-shaped relationship between alcohol consumption, incident cardiovascular disease, and total and cardiovascular disease deaths. As compared with abstainers, alcohol intake of 5 to 15 g/day was associated with 26%, 35%, and 51% reduction of cardiovascular risk, total mortality, and cardiovascular death, respectively. Taken together, these evidences support the cardiovascular benefits of moderate alcohol consumption in most populations, with a dose-response relationship traditionally mirrored by a "J-shaped" curve, where a moderate alcohol intake (10 to 30 g/day) is beneficial, while no intake or excessive intake (>30 g/day) might be harmful.[5,17] Di Calstelnuovo and colleagues recently published a meta-analysis of alcohol consumption and all-cause mortality including 34 prospective studies and more than one million subjects. The strong J-shaped relationship between all-cause mortality and alcohol intake was strongly reaffirmed.[18]

Interestingly, the type of alcoholic beverage was not associated with a different risk for cardiovascular disease in 38,077 US male health professionals over 12 years of follow-up.[10,19] Similar mortality risk reductions were also observed with red wine, white wine, other types of wine, and combinations of wine types in a further study,[11] so that it was concluded that the risk might be more strongly related to the drinking pattern than to the type of alcoholic drink.[20] At variance with these findings, important evidences in support of the cardioprotective effect of red wine arise from experimental studies evaluating the acute intake of dealcoholized red wine. Karatzi and colleagues investigated the acute intake of 250 mL dealcoholized red wine in men with angiographically documented coronary disease, and found decreased arterial stiffness and improved augmentation index, as derived from arterial wave reflection patterns.[21] In a further study the same authors observed that an identical dose of dealcoholized red wine decreased adverse postsmoking arterial wave reflections and lessened the rise in

systolic blood pressure.[22] Therefore, it seems reasonable to conclude that the beneficial effects of alcohol might be greatly amplified by additional compounds present in red wines.[23]

Biological effects

The main ingredients of grapes are water and sugar. Nevertheless, more than 500 compounds have been recognized in dealcoholized wine, its main commercial derivative.[24] Polyphenolic compounds give wines color and account for differences in flavor between reds and whites (their concentration is in fact much lower in white wines, being 0.01% versus 0.2% in red wines). They basically come from the fruit (skins and seeds) and vine stems. The more represented phenol groups in wine are flavonoids and nonflavonoids, which are again present in a larger amount in red than in white wines, and include free and conjugated myricetin, quercetin, kaempferol, and isorhamnetin; (+)-catechin, (−)-epicatechin, gallic acid, p-coumaric acid, caffeic acid, caftaric acid, trans-resveratrol, cis-resveratrol, and trans-resveratrol glucoside.[25] In red grapes, the main flavonol is quercetin (mean = 44%), followed by myricetin (37%), kaempferol (6.4%), laricitrin (5.6%), isorhamnetin (3.9%), and syringetin (3.2%). In white grapes, the main flavonol was quercetin (mean = 81%), followed by kaempferol (17%) and isorhamnetin (1.7%). The delphinidin-like flavonols myricetin, laricitrin, and syringetin were missing in all white varieties, indicating that the enzyme flavonoid 3′,5′-hydroxylase is not expressed in white grape varieties.[26] Resveratrol (3, 4′, 5 trihydroxystilbene) is a naturally occurring phytoalexin released by spermatophytes in response to injury. It mainly occurs in grape berry skins but not in flesh, and the final concentration is dependent upon the fermentation time. Therefore, since white wines are traditionally subjected to a shorter maceration time, they contains a lower amount of this compound.[27] The concentration of the trans-isomer of resveratrol also vary widely in red wines, and depends mostly on grape cultivar, geographical origin, wine type, Botrytis infection, and enological practices. The highest concentrations of resveratrol are traditionally observed in red wines from France (Beaujolais, Midi, Rhône, Bordeaux, Burgundy), Spain (Pinot Noir, Merlot, Grenache), Italy (Aglianico, Piedirosso), and the US (Muscadine).[27,28]

A number of experimental studies suggest that the red wine compounds, especially polyphenols, alcohol, and resveratrol, might play a valuable role for preventing development and progression of atherosclerosis, acting through a variety of beneficial pathways that include inhibition of lipid peroxidation (lipoproteins, membranes), chelation of copper, free-radical scavenging, alteration of eicosanoid synthesis, inhibition of platelet aggregation, anti-inflammatory activity, improvement of endothelial function, lowering of blood pressure, vasorelaxing activity, modulation of lipoprotein metabolism, activation of proteins that prevent cell senescence, anticancer and estrogenic activity (Figure 1).[29,30]

The antioxidant properties of grape polyphenols are likely to be pivotal to their cardioprotective effects, which are mediated by cellular signaling and interactions at the genomic level. Red wine is a natural source of antioxidants, which may protect the body from oxidative disorders, and most of these effects have been ascribed to resveratrol. Micallef and colleagues observed that a 400 ml/day intake of red wine for two weeks significantly increased antioxidant status and decreased oxidative stress.[31] Likewise, healthy volunteers consuming 375 ml red wine daily for two weeks had an increased concentration of plasma total phenolic. Similarly, the maximum concentrations of conjugated dienes and thiobarbituric acid-reactive substances in Cu-oxidized low-density lipoprotein cholesterol (LDL-C) were reduced, while plasma high-density lipoprotein cholesterol (HDL-C) concentrations increased.[32] Some experimental studies suggested that resveratrol protects atherogenic lipoprotein particles from oxidative modifications,[33–35] enhances cholesterol efflux from vessel wall, and reduces cholesterol influx or uptake in macrophages.[35] Since all these aspects strongly contribute to atherogenesis, resveratrol has been suggested as a natural antioxidant that protects against cardiovascular damage. Nevertheless, a number of high profile publications have also completely misrepresented the effects of resveratrol.[36,37] Basically, the doses employed in animal studies to show health benefits would require human consumption of thousands of liters of wine per day. Other natural antioxidant present in the grapes, especially viniferin, quercetin, and catechin, also inhibit various cyclooxygenase enzymes, which play an important role in inflammatory disorders, including atherosclerosis.[38]

An additional target of red wine and its milieu of beneficial components is the endothelia. Endothelial dysfunction is a hallmark of atherosclerosis, retaining also prognostic implications for cardiovascular risk. Accordingly, a variety of biological and clinical studies have demonstrated that red wine components can produce coronary vasodilation, induce expression of several cardioprotective oxidative stress-inducible proteins, and activation of adenosine receptors[39] improve brachial flow-mediated dilatation.[40,41] The leading mechanism underlying improved endothelial function with regular moderate wine intake is an increase

of nitric oxide synthesis,[42] most likely due to a remarkable increase of nitric oxide synthase promotor activity.[43] Corder and colleagues also suggested that procyanidins might have a specific effect within blood vessels that is distinct from any antioxidant properties. This biological mechanism was identified as a reduction of endothelin-1 synthesis.[44] In line with this finding, Corder also noticed that in areas in which there was a high number of people aged 90 years or more, local wines had special characteristics such as high procyanidin contents.[45]

Among the kaleidoscope of beneficial effects associated with a moderate intake of red wine, modulation of platelet function is probably the most investigated and certain. Basically, a moderate intake of alcohol (~30 g/day) from red wine decreases collagen-induced platelet aggregation.[46] Likewise, consumption of nonalcoholic components either from 320 mL of red wine or from dealcoholized red wine determines an increase in polyunsaturated fatty acids in all phospholipid fractions of platelets, an important antioxidant effect.[46] Collagen-induced platelet aggregation was also significantly reduced in subjects consuming two to four drinks per day of red wine,[47] and a flavanol-rich grapeseed extract acutely decreased epinephrine and adenosine diphosphate-stimulated platelet reactivity.[48]

Similar beneficial effects of red wine components were reported on blood coagulation. A meta-analysis of experimental studies showed that a moderate dose of alcohol (30 g/day) increased the concentrations of plasma HDL-C, apolipoprotein A-I, plasminogen, tissue plasminogen activator (tPA), whereas it also decreased lipoprotein(a), fibrinogen and von Willebrand Factor (VWF).[49] In the Framingham Offspring Study, moderate alcohol intake was associated with lower levels of fibrinogen, plasma viscosity, vWF, and factor VII.[50] In a large epidemiological study, including over 3,000 men, daily alcohol consumption showed a positive dose-response relationship with HDL-C and tPA, and a negative dose-response relationship with fibrinogen, VWF, and D-dimer.[51]

The effect of moderate alcohol consumption on blood pressure is currently uncertain. In a meta-analysis of randomized controlled trials to assess the effects of alcohol reduction on blood pressure including 15 randomized controlled trials,

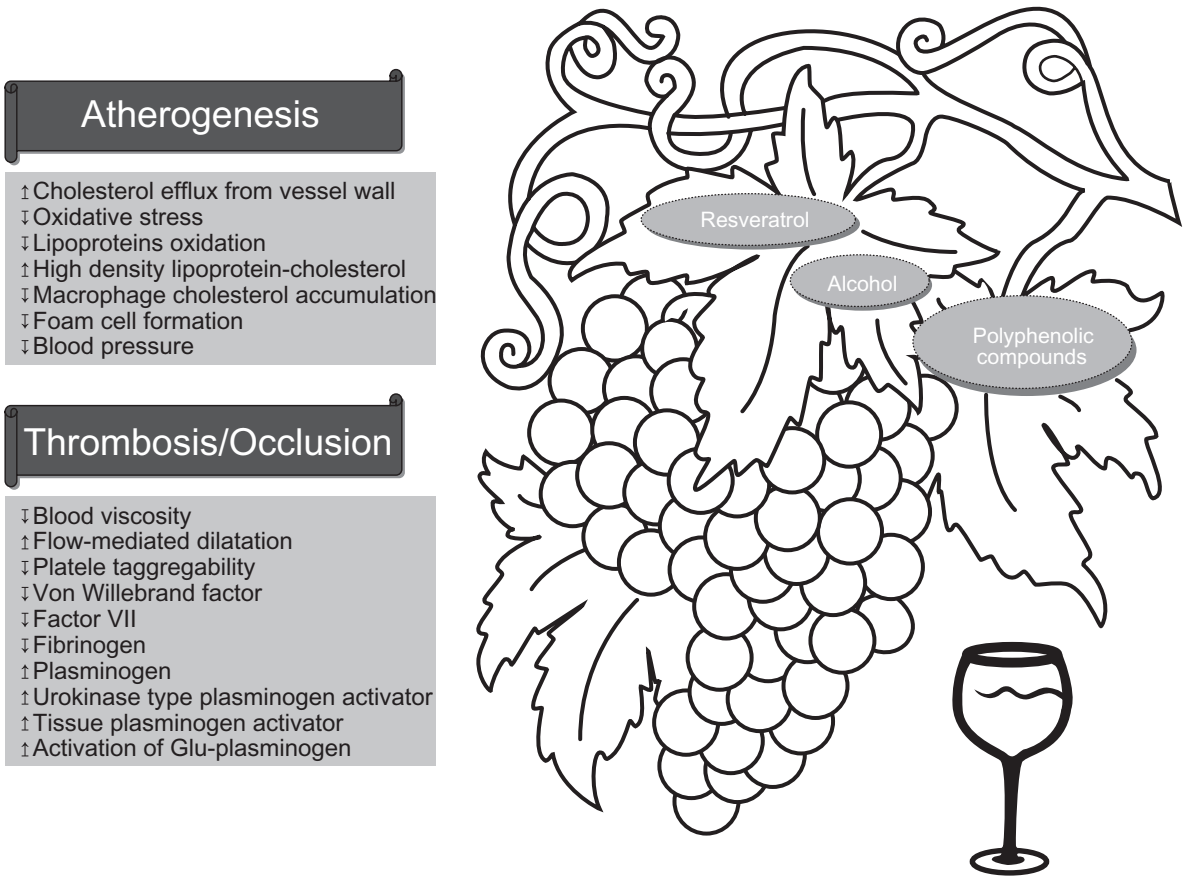

Figure 1 Beneficial effects of red wine components on cardiovascular health.

alcohol reduction was associated with a significant reduction in mean systolic and diastolic blood pressures of –3 mmHg and –2 mmHg, respectively.[52] Although a J-shaped or linear association between alcohol consumption and blood pressure has also been reported in other observational epidemiological studies,[53–55] other controlled clinical studies testing the effects of alcohol intake on blood pressure produced inconsistent results, as highlighted in a systematic review of trials that measured blood pressure after a period of sustained alcohol intake.[56]

Some investigations have examined the relationship between alcohol consumption and insulin sensitivity in non-diabetic and diabetic subjects,[57–64] concluding that moderate alcohol and red wine intake produces potentially beneficial modulations of insulin sensitivity and showed an inverse association with the risk of incident type 2 diabetes. One last mechanism responsible for the French Paradox may be related to an increase of marine omega-3 fatty acids concentration in blood (an effect they termed "fish-like effect" of wine), since long chain omega-3 fatty acids are known to protect against cardiovascular complications, to reduce inflammation, and to limit severe cardiac arrhythmias.[65,66]

Conclusions

For equal total alcohol intake, men and women drinking red wine have lower mortality than white wine, beer or other drinkers. Nevertheless, despite mounting evidence that moderate red wine intake is beneficial and that it might be "paradoxically" considered a therapeutic option to prevent or even treat coronary disease, some doubts still remain. First, it is still unclear whether the positive benefits are biased by some socioeconomic confounders (eg, age, gender, smoking habits, drinking pattern, physical activity). Then, the cardio-protective effects appear somehow greater among middle-aged and elderly adults than among young adults. While the J-shaped association between alcohol intake and mortality is well established, the nadir of the curve is not determined, as well as the amount of alcohol needed to lower the risk of coronary disease is also uncertain, since most studies reported an overall effect between one and three glasses of wine. The most effective substances for preventing coronary disease are also to be definitely identified; while there is a widespread agreement on the powerful antioxidant effects of polyphenols, the biological role of resveratrol is still controversial, especially because as many red wines contain negligible amounts of it and,[67,68] and some winemakers have already been drawn down the route of attempting to increase resveratrol levels in their wine, thereby focusing on focus on the tannin components. The bioactivity of metabolites derived from wine, and their accumulation in vital organs are still under investigation, but there are high expectations of positive results. Finally, due to the heterogeneous concentration of alcohol, resveratrol and polyphenols in the different grapes, it is still to be established whether certain variety of wines might be more beneficial than others. All these issues should be definitely cleared before recommending abstainers to initiate light to moderate consumption of red wine.

Disclosures

The authors report no conflicts of interest in this work.

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