

## Scientific Evidence in Support of the Health Benefits of Wine

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### Abstract

A large number of epidemiological studies carried out since the early 1980s have shown that the consumption of wine, particularly of red wine, helps to prevent coronary heart disease and some cancers. Evidence from a recently published meta-analysis of 13 studies (involving 209,418 subjects) on the relationship between wine consumption and risk of cardiovascular disease has revealed an average significant reduction of 32% of overall vascular risk associated with moderate (1-2 drinks or 150-300 mL/day) versus no wine consumption. From 10 studies involving 176,042 persons there was strong evidence to support a J-shaped relationship between different amounts of wine intake and vascular risk, suggesting that light to moderate wine drinkers have lower vascular risk than either heavier drinkers or non-drinkers. Wines, especially red wines, contain about 1800-3000 mg/L of polyphenolic compounds, most of which are potent antioxidants and are therefore thought to function as cardioprotectives and anti-carcinogens. It has been shown that flavonoids (flavonols, anthocyanins, catechins and pro-anthocyanidins) as well as non-flavonoids from red wine strongly inhibit low-density lipoprotein oxidation, eicosanoid synthesis, and platelet aggregation, which are significant steps in reducing coronary heart disease mortality. For some polyphenols, an anticarcinogenic function has also been suggested, and a few studies in cell lines and animal models have shown that some wine polyphenols may affect molecular events in the initiation, promotion, and progression of some cancers.

## WINE CONSUMPTION AND RISK OF CARDIOVASCULAR DISEASE

### Epidemiological Evidence

Studies of wine and its effects on health have a long history, ranging from anecdotal accounts in ancient times to more recent rigorous studies of populations with hundreds of thousands of participants (Rimm and Stampfer, 2002; de Gaetano et al., 2002). Most studies suggest that men and women who drink 1 to 2 drinks per day on average have lower total mortality rates, reflected in lower incidence of coronary heart disease (Di Castelnuovo et al., 2002), diabetes (Ajani et al., 2000, Wannamethee et al., 2003.), ischemic stroke (Reynolds et al., 2003) and in some populations prostate cancer (Schoonen et al., 2005) and dementia (Mukamal et al., 2003).

The benefit of moderate alcohol consumption on risk of coronary disease has been documented in almost 100 studies (Rimm and Stampfer, 2002). Evidence from a recently published meta-analysis of 13 studies (involving 209,418 subjects) on the relationship between wine consumption and risk of cardiovascular disease (CVD) has revealed an average significant reduction of 32% of overall vascular risk associated with moderate (1-2 drinks or 150-300 mL/day) versus no wine consumption (Di Castelnuovo et al., 2002). Interestingly, in studies with men only, the protection offered by wine was relatively small (13%) and not significant; in contrast, in studies with both sexes the protection was 47%. Whether women are more susceptible to the benefit of wine or if they are more likely to drink lower amounts, thus capturing its maximal advantage, remains to be established.

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Wine contains 8% - 15% ethanol by weight, and epidemiological evidence confirm an association between moderate alcohol intake and a reduced risk of coronary heart disease (CHD) in populations. A meta-analysis of 51 epidemiological studies (Corrao et al., 2000) concluded that the protective effects of alcohol were most pronounced at moderate doses. The risk of CHD decreased by 20% when 0 to 2 drinks of alcohol were consumed per day. One of the most important modifications with regular alcohol consumption is an increase in plasma levels of high-density lipoprotein (HDL) (De Oliveira et al., 2000). A meta-analysis examining the effect of moderate alcohol intake on lipids (not differentiating between the type of alcoholic beverage consumed) found that a 16.8% reduction in risk of CHD could be directly attributable to increased HDL concentration from the consumption of 30 g of alcohol (2.5 drinks) per day (Rimm et al., 1999). One to two drinks per day of any alcoholic beverage increases HDL by 12% on average (Linn et al., 1993).

### **In Vitro and In Vivo Studies**

Thus, epidemiological studies provide the initial evidence suggesting moderate wine consumption is associated with a reduction in cardiovascular risk. A second type of evidence that continues to emerge relates to biological plausibility (Goldberg, 2003). This evidence includes in vitro studies, studies in animal models of human disease, and measures of surrogate markers of disease in humans. Thus, a series of in vitro and in vivo studies suggest that the polyphenolic compounds in red wine, in addition to ethanol, may play an active role in limiting the initiation and progression of atherosclerosis.

Polyphenolic substances in wine are usually subdivided into two groups, the flavonoids (flavonols, anthocyanins, catechins and pro-anthocyanidins) and non-flavonoids (Mazza, 1995). The most common flavonoids in red wine are anthocyanins, flavonols such as quercetin and flavan-3-ols such as tannins and catechin (Mazza and Miniati, 1993; Howard and Kritchevsky, 1997). The nonflavonoids include hydroxybenzoates, hydroxycinnamates and stilbenes, and the most significant compounds in this group in terms of possible positive health benefits are the stilbene resveratrol (Waterhouse and Teissedre, 1997; Soleas et al., 1997) and the related compounds piceid and astringin.

Many studies have shown that flavonoids have protective effects against the initiation and progression of atherosclerosis. Flavonoids from red wine and purple grape juice inhibit in vivo platelet-mediated experimental coronary thrombosis (Demrow and Folts, 1995). They also inhibit ex vivo platelet aggregation in humans (Folts, 1998). Grape flavonoids increase the release of nitric oxide and decrease the production of super oxide in aggregating platelets, which limits the size of a developing platelet aggregate (Freedman et al., 2001).

In in-vitro studies with phenolics in red wine and normal human low-density lipoprotein (LDL) showed that red wine inhibits the copper-catalysed oxidation of LDL (Frankel et al., 1993). Two possible mechanisms for this action were advanced, i.e., that phenolic compounds complex with  $\text{Cu}^{++}$  to reduce it to  $\text{Cu}^+$ , which may in turn reduce hydroperoxides, and that during the LDL peroxidation, phenols in wine may act as self-regenerating reducing compounds. Therefore, these authors concluded that with regular ingestion of these antioxidant phenols via red wine consumption, a collective reduction in the oxidation of lipoproteins may occur and thus contribute to reduced atherosclerosis and morbidity and mortality from CVD.

Grape flavonoids also protect and increase serum HDL paroxonase by reducing macrophage oxidative stress through inhibition of cellular oxygenases such as NADPH oxidase, or myeloperoxidase (Fuhrman and Aviram, 2001).

From a comparison of in vitro effects of red wine, white wine and ethanol on cell mediated oxidation of LDL and HDL by three frequently-used assays Vincent et al. (1999)

reported that red wine (0.2 mg ethanol/mL) inhibited LDL oxidation as indicated by an 85.7% decrease in absorbance at 234 nm, a 96.5% decrease in TBARS production and complete prevention of the decrease in TNBS reactivity. White wine and ethanol did not have any significant effect at 0.2 mg/mL. White wine at 1.0 mg ethanol/mL inhibited TBARS production from LDL by 84.1%. Red wine (0.2 mg ethanol/mL) inhibited HDL oxidation as indicated by a 78.9% decrease in  $\Delta A_{234}$ , an 81.7% decrease in TBARS production and by no change in TNBS reactivity. The authors concluded that red wine inhibits the cell mediated oxidation of lipoproteins, that white wine is not as effective as red wine and that the effect of the red wine is not due to its ethanol content.

Numerous studies with dogs, monkeys, rabbits and hamsters have shown that red wine may inhibit the initiation of atherosclerosis by one or more of the following mechanisms: platelet activation, oxidative modification of LDL, endothelial dysfunction, and inflammation (Folts, 2002).

Nigdikar et al. (1998) compared red wine (375 mL/d), white wine (375 mL/d), red wine polyphenols (1 g/d, equivalent to 375 mL red wine/d) in capsules, red wine polyphenols (1 g/d) dissolved in white wine, and a control alcoholic drink (40 g ethanol/d) on LDL oxidation in 6-9 healthy men for 2 weeks. Analyses of the results (Table 1) showed no significant differences among any of the groups treated with the various red wine polyphenol forms. There was, however, a significant difference observed between the groups treated with white wine and the control drink vs. those treated with the various red wine polyphenol forms. These results led the authors to conclude that red wine consumption increases plasma and LDL polyphenols; in addition to enhancing the antioxidant activity that was shown by decreased plasma total peroxides, increased lag time and decreased lipid peroxides in the copper-catalyzed peroxidation of LDL-conjugated dienes. It can therefore be extrapolated that decreasing LDL oxidation through the consumption of red wine may prevent the development of CVD.

In a more recent study by Caccetta et al. (2000) 12 healthy male nonsmokers consumed red wine, phenol-stripped red wine, dealcoholized red wine, or water, each at a separate visit, in random order and one week apart. Beverages were consumed over 30 min and blood was sampled just before beverage consumption and 1, 2, and 4 h after consumption. Copper-induced serum and LDL oxidizability *ex vivo*, together with serum uric acid, and plasma caffeic, protocatechuic, and 4-*O*-methylgallic acids were measured.

The results showed that consumption of red wine or dealcoholized red wine significantly increased plasma phenolic acid concentrations. Red wine (whether dealcoholized, phenol stripped, or as is) also caused a significant elevation in serum uric acid. Despite these changes, there was no effect on *ex vivo* lipoprotein oxidation over a 4-h time period. The results are not in agreement with other research findings in which the consumption of red wine decreased LDL oxidation in humans (Frankel et al., 1993; Nigdikar et al. 1998). These differences reflect the complexity of potential mechanisms exhibited by wine polyphenolic *in vivo*. Caccetta et al. (2000) provided an alternative hypothesis regarding the benefits seen from consumption of different beverages, stating that evidence exists that alcohol consumption can induce oxidative stress through free radical formation, which interferes with antioxidant defense mechanisms, or by interfering with enzymes involved in the antioxidation process. These authors suggest that the overall effect of alcoholic beverages on LDL oxidation may be a balance between two factors, namely, the pro-oxidant and antioxidant components of the beverages consumed. The authors concluded that although the consumption of both regular and dealcoholized red wine significantly increased the plasma concentrations of phenolic acids, there was no effect on LDL oxidation over the 4-h time period studied. Obviously, the question arises whether a 4-h time period is adequate for measuring LDL oxidation effects. Longer-term controlled studies are required to better understand the effects and mechanisms of wine polyphenolic compounds.

### **Controlled Clinical Trials**

Recently, Tsang et al. (2005) investigated the effects of moderate red wine consumption on the antioxidant status and indices of lipid peroxidation and oxidative stress associated with CHD. They performed a randomised, controlled study with 20 free-living healthy volunteers in which subjects in the red wine group consumed 375 mL red wine (young vatted Cabernet Sauvignon, 12% alcohol) daily for 2 weeks, and measured the total concentration of phenolics and analysed the individual phenolics in the wine and plasma by HPLC with tandem MS. The antioxidant capacity of plasma was measured with electron spin resonance spectroscopy while homocysteine and fasting plasma lipids were also determined. The production of conjugated dienes and thiobarbituric acid-reactive substances (TBARS) were measured in Cu-oxidised LDL. Plasma total phenolic concentrations increased significantly after 2 weeks of daily red wine consumption ( $P < 0.001$ ) and trace levels of metabolites, mainly glucuronides and methyl glucuronides of (+)-catechin and (-)-epicatechin, were detected in the plasma of the red wine group. These flavan-3-ol metabolites were not detected in plasma from the control group. The maximum concentrations of conjugated dienes and TBARS in Cu-oxidised LDL were reduced ( $P < 0.05$ ) and HDL cholesterol concentrations increased ( $P < 0.05$ ) following red wine consumption. These findings provide some evidence for potential protective effects of moderate consumption of red wine in healthy volunteers.

A randomized, crossover, single-blind trial by Estruch et al. (2004) evaluated the effects of wine and gin on inflammatory biomarkers of atherosclerosis. Forty healthy men (mean age, 37.6 years) consumed 30 g ethanol per day as either wine or gin for 28 days. Before and after each intervention, they measured the expression of lymphocyte function-associated antigen 1 (LFA-1), Mac-1, very late activation antigen 4 (VLA-4), and monocyte chemoattractant protein (MCP-1) in monocytes, as well as the soluble vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), interleukin-1alpha (IL-1alpha), C-reactive protein (hs-CRP) and fibrinogen. The results showed that after either gin or wine consumption, plasma fibrinogen decreased by 5 and 9%, respectively, and cytokine IL-1alpha by 23 and 21%. The expression of LFA-1 (-27%), Mac-1 (-27%), VLA-4 (-32%) and MCP-1 (-46%) decreased significantly after wine, but not after gin. Wine reduced the serum concentrations of hs-CRP (-21%), VCAM-1 (-17%) and ICAM-1 (-9%). Thus, both wine and gin showed anti-inflammatory effects by reducing plasma fibrinogen and IL-1alpha levels. However, wine had the additional effect of decreasing hs-CRP, as well as monocyte and endothelial adhesion molecules.

### **OTHER WINE/ALCOHOL HEALTH ASSOCIATIONS**

In addition to the negative association between wine/alcohol consumption and mortality from coronary heart disease that has now been observed in many studies, some epidemiological studies have associated alcohol or wine consumption with reduced rates of incidence of several other diseases. These include prostate cancer (Schoonen et al., 2005), diabetes (Ajani et al., 2000, Wannamethee et al., 2003.), ischemic stroke (Reynolds et al., 2003), and dementia and Alzheimer's disease (Mukamal et al., 2003).

#### **Prostate Cancer**

Prostate cancer is the second leading cause of cancer deaths after lung cancer in men. In a recent study by Schoonen et al. (2005), data from a population-based case control study were utilized to evaluate the association of alcohol consumption with prostate cancer in middle-aged men. A total of 753 newly diagnosed prostate cancer cases, 40–64 years of age, participated in the study. An equal number of subjects, matched to cases by age, were selected through random digit dialing. All participants completed an in-person interview on lifetime alcohol consumption and other risk factors for prostate cancer. Regression models were used to estimate odds ratios (OR) and assess significance (95% confidence intervals [CI]). No clear association with prostate cancer risk was seen for overall alcohol consumption. Each additional glass of red wine consumed per week

showed a statistically significant 6% decrease in relative risk, and there was evidence for a decline in risk estimates across increasing categories of red wine intake (trend  $P < 0.02$ ). No clear associations were seen for consumption of beer or liquor. This study suggests that there may be a reduced relative risk associated with increasing level of red wine consumption. These finding, however, must be viewed with caution as the number of subjects was relatively small, and other studies (Dennis, 2000; Dennis and Hayes, 2001) have reported inconsistent results on the association of moderate alcohol/wine consumption and reduced risk of prostate cancer. Further research is needed to evaluate the potential negative association between red wine intake and prostate cancer risk.

### **Type 2 Diabetes**

Similarly, a variety of studies of alcohol intake and risk of type 2 diabetes mellitus have been conducted and produced conflicting results. Some, but not all studies have implicated heavy drinking as a risk factor for type 2 diabetes mellitus (Balkau et al., 1991; Wei et al., 2000). Conversely, several recent prospective studies mainly conducted in men have suggested that light to moderate drinking may be inversely associated with the development of type 2 diabetes mellitus (Rimm et al., 1995; Tsumara et al., 1999; Ajani et al., 2000). In the Physicians' prospective cohort health study, involving 20,951 participants and 766 cases of type 2 diabetes mellitus, healthy men who self-select for light to moderate alcohol consumption had a decreased subsequent risk of diabetes mellitus (Ajani et al., 2000). After adjustment for age, smoking, physical activity, and body mass index, the relative risk estimates for those reporting alcohol use of rarely/never, 1 to 3 drinks per month, 1 drink per week, 2 to 4 drinks per week, 5 to 6 drinks per week, and 1 or more drinks per day were 1.00 (referent), 1.03, 0.89, 0.74, 0.67, and 0.57, respectively ( $P < .001$ ) (Ajani et al., 2000). In the San Antonio Heart Study (Wei et al., 2000) alcohol consumption was positively associated with risk of diabetes mellitus in men, but not in women.

### **Dementia**

Recent epidemiological studies suggest that moderate alcohol intake may benefit cognition. For example, the Epidemiology of Vascular Aging Study (participants aged 59–71 years; 59 percent female) found that mean scores on the Mini-Mental State Examination, a measure of global cognitive function, were higher among women reporting moderate levels of alcohol intake compared with no intake (Dufouil et al., 1997). The Atherosclerosis Risk in Communities Study (subjects aged 45–69 years; 55 percent female) found that drinkers who drank lightly to moderately, had higher cognitive scores than nondrinkers on three cognitive tests, with a clear dose-response association on a word fluency test and an inverted U-shaped response on delayed word recall and digit symbol substitution tests (Elias et al., 1999).

A case-control study conducted within the Cardiovascular Health Study (participants aged 65–97 years; 60 percent female) found that the odds ratio for incident dementia was 0.37 (or 63% reduction) for subjects reporting consumption of 1–6 drinks per week compared with nondrinkers; for those reporting 7–13 drinks per week, the odds ratio was 0.64 (Mukamal et al., 2003). Similarly, the Rotterdam Study (participants aged 60–90 years; 52 percent female) reported hazard ratios for dementia (relative to nondrinkers) of 0.82 for  $< 1$  drink per week, 0.75 for 1–6 drinks per week, and 0.58 for 1–3 drinks per day (Ruitenberg et al., 2002). A positive relationship, however, has not been detected consistently. For example, the Established Populations for Epidemiologic Studies of the Elderly program (subjects aged  $\geq 65$  years; 56 percent female) reported an odds ratio of 1.1 (i.e. 10% increase) for Alzheimer's disease comparing consumption of 28.3 g of alcohol per day with no consumption (Hebert et al., 1993). Thus, it appears that moderate levels of alcohol intake may be associated with better cognition and reduced risk of significant cognitive decline; however, confounding associations with unmeasured factors cannot be ruled out.

## CONCLUDING REMARKS

Epidemiological studies and recent *in vitro* and *in vivo* data indicate that moderate daily intake of wine (1-2 drinks a day) may reduce the risk of developing CHD and stroke.

Other positive effects of wine on health such as decreasing the risk of certain cancers and Alzheimer's disease remain to be established. Red wine, which has a higher content of phenolics appears to be superior to white wine and other alcoholic beverages protecting against CHD and stroke. However, in this era of evidence-based medicine, a large-scale randomized control trial, assessing the effects of red wine intake versus a non-alcoholic placebo, would be required to ensure that there is legitimacy to both the epidemiological and biological data. Only based on the favourable results of such a study may health professionals be fully justified in recommending the consumption of red wine for cardiovascular protection. In the mean time, my advise is to drink wine moderately to health, and perhaps for health!

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## Tables

Table 1. Comparison of red and white wine, red wine polyphenols and an alcoholic drink on plasma and LDL-associated antioxidant effects<sup>1</sup>.

Supplement	Plasma polyphenols	Plasma lipid peroxides	LDL polyphenols	LDL peroxidation lag time	LDL conjugated-diene formation	LDL lipid peroxides	LDL peroxidation lag time
Red wine	↑ 38%	↓ 32%	↑ 26%	↑ 31%	↓ 15%	↓ 22%	↑ 31%
White wine	No change	↑ 23%	Not reported	Not reported	↑ 14%	Not reported	Not reported
White wine + polyphenol powder	↑ 27%	↓ 29%	↑ 62%	↑ 21%	↓ 11%	↓ 23%	↑ 21%
Polyphenol powder capsules	↑ 28%	↓ 28%	↑ 29%	↑ 27%	↓ 12%	↓ 25%	↑ 27%
Alcoholic drink	No oxidative or antioxidative effects were observed after the control drink						

<sup>1</sup> Data adapted from Nigdikar et al., 1998.

