Red Wine and Cardiovascular Health
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There is strong epidemiological evidence that light-to-moderate consumption of alcoholic drinks, but neither zero nor more than moderate intake, reduces mortality from all causes and also diminishes cardiovascular risk.1 The lowest risk for coronary heart disease mortality is seen with 1 to 2 drinks (12.5–25 g alcohol) per day.

**Article, see p 1065**

Hypertension is a major risk factor for cardiovascular disease, and there is a clear inverse relationship between light-to-moderate alcohol intake and blood pressure. Thus, the reduced cardiovascular risk associated with moderate consumption of alcoholic drinks may be due, in part, to a reduction in blood pressure. The greatest blood pressure benefit seems to be obtained with 1 drink per day for women and with 2 drinks per day for men.2

In most published studies, red wine has been used as the alcoholic test beverage. Red wine produces concentration-dependent vasodilator effects in subcutaneous small resistance arteries obtained from patients with essential hypertension.3 In addition, red wine and dealcoholized red wine increase flow-mediated vasodilation of the brachial artery in healthy subjects.4,5 Intake of red wine also counteracts endothelial dysfunction produced by high-fat diet in human volunteers,4 and red wine increases flow-mediated vasodilation and decreases blood pressure in adult cigarette smokers.7,8

**Alcohol Versus Polyphenols in Red Wine**

With red wine, both the alcoholic and the polyphenolic components seem to contribute to its beneficial effects.9 The alcoholic component is known to increase high-density lipoprotein cholesterol and to decrease fibrinogen concentrations.10 The polyphenols present in red wine have been shown to provide beneficial effects by inhibiting prooxidant enzyme systems and by stimulating antioxidant enzyme systems in the vasculature (Figure). In addition, wine polyphenols inhibit platelet aggregation, attenuate vascular inflammation, and improve endothelial function.9

In the current issue of *Circulation Research*, Chiva-Blanch et al11 demonstrate in a small prospective clinical study that a reasonable daily dose of dealcoholized red wine (275 mL/day) decreases systolic and diastolic blood pressures. This finding is in agreement with previous findings showing that the vasodilator effects of red wine may be mediated, at least in part, by polyphenolic compounds.4 Also other nonalcoholic, polyphenol-rich beverages such as grape juice produce vasodilation (increase flow-mediated vasodilation) in healthy individuals.12

Cardiovascular risk factors are associated with oxidative stress in the vasculature because of an increased production and/or impaired inactivation of reactive oxygen species.13,14 Oxidative stress, particularly the increased vascular production of superoxide, rapidly oxidizes and inactivates bioactive NO. In addition, there is evidence that persisting oxidative stress can render endothelial NO synthase (eNOS) dysfunctional such that it no longer produces NO but superoxide.11,14 This is likely to represent the pathophysiological situations of the subjects participating in the current study by Chiva-Blanch et al.11 All these individuals had several cardiovascular risk factors.

**Red Wine Polyphenols Reduce Oxidative Stress and Increase Bioactive NO in the Vasculature**

When the effects of 3 alcoholic beverages, red wine, beer, and vodka, were compared in a recent study,15 only red wine provided protection against vascular oxidative stress. Indeed, red wine polyphenols seem to shield the vasculature by reducing reactive oxygen species (eg, by decreasing the expression of p22phox) and by inhibiting endothelin-1 expression.16-18 At the same time, red wine polyphenols have been shown to increase bioactive NO in the vasculature. Also other protective factors, such as endothelium-derived hyperpolarizing factor, are stimulated.16 In the current study by Chiva-Blanch et al,11 the decrease in blood pressure by dealcoholized red wine was associated with elevated plasma levels of nitrite and nitrate, the oxidation products of NO. Thus, the study supports the notion that, also in humans in vivo, polyphenolic compounds from red wine can improve the functionality and activity of eNOS and can increase vascular levels of NO. Although a causal relationship between this effect and the observed decrease in blood pressure seems plausible, it is not being demonstrated in the study by Chiva-Blanch et al.11

**Resveratrol and More**

Red wine is a complex mixture containing numerous phenolic compounds. This raises the question of the chemical entities actually responsible for the beneficial effects. There is evidence that particularly the phytoalexin resveratrol can provide health benefits.19 Experimentally, many positive effects of red wine can be mimicked with (usually relatively high doses of) resveratrol.20 For instance, both red wine21 and resveratrol22 have been shown to enhance eNOS expression in cultured human endothelial cells. However, the effect of red wine cannot be explained by resveratrol alone; it is largely mediated by...
resveratrol (≈70%), but several other polyphenols and phenolic acids contribute.21 Also, both red wine and resveratrol enhance eNOS enzymatic activity. Whereas the effect of resveratrol on eNOS phosphorylation (and activation) mainly involves estrogen receptor–mediated activation of extracellular signal-regulated kinases 1 and 2,24 the phosphorylation (and activation) of eNOS by phenolic extracts from red wine also involves the phosphatidylinositol 3-kinases/Akt pathway.25 Resveratrol has a low bioavailability.19 Therefore, many in vivo effects of red wine are likely to be attributable to resveratrol metabolites in concert with several other polyphenolic compounds (and possibly their metabolites).

**Red Wine and Unresolved Questions**

The beneficial effects of red wine can be enhanced by a healthy diet. Indeed, a synergistic effect of red wine and green olive oil (both are components of the Mediterranean diet) on flow-mediated vasodilation has been demonstrated.26 The average moderate wine drinker is more likely to exercise, to be health conscious, and to be of a higher educational and socioeconomic status.9 Nevertheless, there is growing evidence, corroborated by the current study of Chiva-Blanch et al,11 that chemical constituents present in red wine confer health benefits beyond alcohol and are independent of potential confounding factors. However, numerous issues need to be resolved to clearly assess the preventive or therapeutic potential of red wine constituents. Specific chemical entities responsible for the beneficial effects have to be identified. In this context, one has to realize that there are probably major differences between different red wines, depending on the grape and the growing area.21 Pharmacological mechanisms leading to increases in vascular NO and other beneficial effects have to be elucidated, and it has to be clarified whether the decrease in blood pressure is causally related to the increased NO levels or what other mechanisms may be involved.

Finally, the question whether white wine offers a similar benefit as red remains unresolved. White wine, which is usually fermented without skin and seeds, is missing many of the polyphenols (eg, resveratrol, catechin, quercetin) mainly found in these parts of the grape. There are a few studies27 demonstrating superior effects of red versus white wine on certain cardiovascular parameters. However, epidemiological evidence demonstrating a specific benefit of red over white wine is poor;27 and conclusive studies comparing the 2 are missing. In the long run, a prospective, randomized study would be needed to prove or drop the red-better-than-white hypothesis.

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None.

**References**


**Figure. Factors potentially contributing to the vasoprotective effects of red wine.** The alcoholic component of red wine increases high-density lipoprotein (HDL) cholesterol level and decreases fibrinogen concentrations. Polyphenols present in red wine independently inhibit platelet aggregation, enhance bioactive NO, stimulate the formation of endothelium-derived hyperpolarizing factor (EDHF), reduce reactive oxygen species (ROS) generation, and inhibit endothelin-1 (ET-1) expression.


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