Does Wine Work?

For more than two decades, evidence has been accumulating that moderate alcohol consumers have lower mortality rates from coronary heart disease (CHD) than do abstainers (1, 2). This cardioprotective effect of alcohol is partly attributable to its ability to increase the concentration of high-density lipoprotein (HDL) cholesterol, a well-defined negative risk factor for CHD (3, 4). Inhibition of platelet aggregation and blood coagulation is another mechanism that may contribute to this beneficial effect (5, 6).

An interesting controversy has developed around the issue as to whether all alcoholic beverages are equivalent in their ability to protect against CHD. Several epidemiological studies based on questionnaires to assess drinking preference have concluded that beverage type does not affect outcome (7, 8). Other publications, based upon equally indirect analyses of per capita CHD mortality and wine consumption on a country-by-country basis, have shown an inverse correlation between these demographic variables (9, 10). The fact that the French, who as a race follow a lifestyle more inclusive of risk factors for CHD (high fat consumption, high frequency of smoking, lower exercise consciousness) than do clean-living North Americans, have a much lower incidence of this disease—a situation appropriately named the "French Paradox" (11)—is proof that there is no justice in death. It is now being postulated that the French are protected against CHD mortality by the large amount of wine they drink, particularly red wine.

What on earth has the color of the wine got to do with it all? A great deal, it seems. The only consistent difference between the red and white wines is that the red contains more phenolic compounds; among these phenols, the major difference is in the flavonoids. No matter that the amount is trivial (1 g/L); the fact is, it is 20-fold the concentration found in the average white wine (12). These flavonoids include compounds such as quercetin, rutin, catechin, and epicatechin, which have been shown in vitro to have powerful biological effects, including inhibition of eicosanoid synthesis (13) and of platelet aggregation (14), as well as of cancer growth and development (15). They are collectively and individually 10–20-fold more potent than vitamin E in protecting low-density lipoproteins (LDL) against oxidation (16), now considered to be a powerful initiating mechanism in the uptake of cholesterol by blood vessels, foam cell formation, and initiation of the "fatty streak," the first step in atherosclerosis (17). The endothelium of blood vessels produces a factor, believed to be nitric oxide, that causes relaxation of the smooth muscle (18). This is now regarded as an important part of the body's defense against atherosclerosis. It has recently been shown, again in vitro, that wine phenolics enhance nitric oxide production and cause vascular relaxation in rat aortic rings (19).

Those of us who eat a decent amount of fruit and vegetables in our diet will ingest a fairly healthy dose of flavonoids, since these compounds are quite widely distributed in the vegetable kingdom. So why the fuss about red wine? Two facts are worth fussing about. First, the addition of two glasses of red wine per day to the average North American diet has been estimated to enhance the flavonoid content of the diet by 40% (20). Second, and more important, the bioavailability of flavonoids in fruits and vegetables has never been clearly established since they have (until recently) never been measured in blood after a normal meal. They are present in complex polymeric and glycosidic forms that may not easily be degraded by digestive juices and, if they are, their relative insolubility in aqueous media may limit or even prevent their absorption. During the fermentation of wine, these aggregates are broken down to monomeric forms, and the 10% or more of alcohol contained in most table wines keeps the flavonoids in stable solution indefinitely in the bottle, and very likely also in the human intestine.

What is the evidence for their absorption in vivo from red wine? The first hopeful experiment in this direction was performed by Klurfeld and Kritchevsky as long ago as 1981 (21). They fed rabbits a high-cholesterol diet for 3 months along with a cheering and equal dose of the following beverages: pure alcohol, beer, whisky, white wine, and red wine. Controls received water alone along with their cholesterol. At the end of the experimental period, the message was clear: Stay away from water at all costs! All of the furry rodents receiving this pristine beverage developed atherosclerotic lesions in the aorta and other major blood vessels; so, too, did the beer-drinking rabbits. Pure alcohol and whiskey reduced the incidence to 75% and 83%, respectively. But the greatest protection against atherosclerosis was provided by the gift of Dionysus: White wine reduced the incidence to 67% and red wine to 40%. Unhappily for rabbits and other laboratory animals, there is no report of this experiment ever having been repeated.

In 1991, Seigneur and colleagues in Bordeaux (where else?) studied 16 male subjects who, over three consecutive periods for 15 days each, received equimolar amounts of alcohol (equivalent to 500 mL of wine), white wine, and red wine (22). At the end of each beverage regime, blood samples were taken for measurement of lipids, platelet coagulation, and various ei-
cosanoids. Alcohol enhanced platelet aggregation, and increased the concentrations of apolipoprotein A-I and LDL-cholesterol. These astonishing results are at variance with most others in the literature. White wine was stated to increase both LDL-cholesterol and HDL-cholesterol. Red wine decreased platelet aggregation and increased HDL-cholesterol. These provocative findings have never been confirmed, and further publications from this group have not come to attention.

An important report from the group at the University of California, Davis, currently in preparation, demonstrates that after administration of 300 mL of red wine containing 80 mg of catechin (the most abundant of the red wine flavanoids), absorption by human subjects can be demonstrated equivalent to 10–20% over the first 3 h, at which time peak concentrations varied from 4.5 to 12 \( \mu \)mol/L. These concentrations were adequate to inhibit LDL peroxidation by >90%. In July of this year, Maxwell et al. (23) reported an increase in serum antioxidant activity, as measured by a chemiluminescent assay, that reached a peak 90 min after ingestion of a standard meal together with 5.7 mL of Bordeaux wine per kilogram of body weight over a 30-min period. Even after 4 h, the antioxidant concentrations in serum were still significantly above baseline (23). In this month’s issue of Clinical Chemistry, a team of investigators from the same University (Birmingham, UK), headed by its Dean of Medicine, Tom Whitehead, but including none of the three authors of the earlier report, describe a similar study in which the antioxidant activity of serum was measured by the same technique in human subjects (24). This activity was increased by a mean of 18% after 1 h and 11% after 2 h by 300 mL of red wine given to nine subjects. An equivalent amount of white wine (given to three subjects) had no effect, and no changes were observed in two control subjects over the same interval; however, four women given 1 g of ascorbic acid increased their serum antioxidant activity by 22% at 1 h and 29% at 2 h. Although the number of subjects and the demographic variables in the different groups were not adequately standardized, and although the same subjects were not exposed to all three nutrients in a randomly rotating manner, this study apparently provides further evidence that wine phenolics can be absorbed by the human intestine in pharmacologically meaningful amounts, albeit at a cost-effectiveness many-fold less than that of vitamin C.

With this in mind, one should ask the following question: Does wine contain a biological component that is present in only limited amounts in a typical diet? Indeed, it does: resveratrol. This trihydroxystilbene is synthesized by \textit{Vitis vinifera}, being present in the canes, leaves, and the skins of the berries. Because these are present during the fermentation of red wines but not white wines, only the former contain significant amounts of resveratrol in the finished product (25). Until recently, this compound was the subject of an obscure and mysterious literature, mainly Japanese, because it was first described as a constituent of herbal folk medicines used for the treatment of lipid, inflammatory, and heart disorders (26). In purified or synthetic form, it was claimed to reduce the synthesis of lipids in rat liver (27), to block the synthesis of eicosanoids in rat leukocytes (28), and to antagonize the antigen-induced contraction of isolated sensitized guinea pig tracheas by a histamine-independent effect that is probably related to arachidonic acid metabolism (29). More recently, in vitro experiments have shown resveratrol to be a powerful inhibitor of platelet aggregation (30), an inhibitor of a protein-tyrosine kinase (31), and an antioxidant more powerful than vitamin E in preventing LDL oxidation, although not as effective as certain other wine flavenoids (32). Investigations by my colleagues and I have shown that its concentration differs widely in red wines, depending on factors such as grape varietal, climate and soil conditions, and vinification techniques (33). Although the concentrations of trans-resveratrol (the only form previously identified in wine) were in most instances rather modest, we and others have subsequently shown the presence in red wines of significant amounts of the cis-isomer as well as the glycosides of both resveratrol isomers (34, 35). Since the latter can be hydrolyzed by glycosidases in the human intestinal tract, about fourfold as much resveratrol as previously thought to be in red wine could be bioavailable; moreover, the cis- and trans-isomers both appear to be biologically active (31). Apart from peanuts (36), no other human-consumed foodstuff contains significant amounts. From the perspective of \textit{Homo sapiens} (and other apes), and excluding peanut eaters, resveratrol is unique to red wine.

A demon demanding exorcism is the notion that it is unwise to recommend a glass or two of wine to someone with a known predisposition to CHD because of its unpredictable metabolic and circulatory effects. In two recent studies, 300 mL of wine (even sweet white wine) consumed with a single light meal had no effect on glucose control, insulin requirements, or triglyceride response in insulin-dependent or non-insulin-dependent diabetics (37, 38). Surely this is the litmus test of wine as a metabolic hazard?

Should we then advocate wine consumption as a health-promoting indulgence? The simple answer is that if every adult North American drank two glasses of wine each day, cardiovascular disease, which accounts for almost 50% of deaths in this population, would be cut by 40%, and $40 billion could be saved annually (39). The nation’s third President, Thomas Jefferson, got it right when he wrote: “I think it is a great error to consider a heavy tax on wines as a tax on luxury; on the contrary, it is a tax on the health of all our citizens.”

I thank my colleagues, George Scolas, Alex Karumanchiri, and Eleftherios Diamandis for their scientific contributions and critical comments. Research support was provided by the National Research Council of Canada (IRAP) and the Wine Council of Ontario.

References


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