Is it time for a wine trial?\textsuperscript{1,2}

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Can wine prevent cardiovascular disease (CVD), the leading cause of death among Americans for the past 90 y? Most epidemiologic studies that have examined wine consumption show reduced CVD mortality in wine consumers, but a specific causal mechanism has not been well established. Results from the Multiple Risk Factor Intervention Trial relating 10-y mortality rates from CVD to plasma cholesterol concentrations were included in the 1990 National Cholesterol Education Program and serve as a "gold standard" for predicting CVD mortality in the United States\textsuperscript{(1)}. However, the Seven Countries studies showed that the relations between plasma cholesterol and CVD mortality are not equivalent among different cultures\textsuperscript{(2)}. The discrepancies led Renaud and de Lorgeril\textsuperscript{(3)} to investigate the effect of wine and to note in their 1992 French Paradox Study that the "alcohol from red wine" was a key to explaining the unexpected low mortality within some populations consuming high-fat diets and having high plasma cholesterol concentrations.

Subsequently, phenolic compounds in red wine were shown to protect plasma lipoproteins from oxidation in vitro\textsuperscript{(4)}, and this antioxidant effect, via many mechanisms, was proposed to explain the reduction in CVD observed in wine drinkers\textsuperscript{(5)} because lipoprotein oxidation is believed to play a causative role in the development of CVD\textsuperscript{(6)}. Nigdikar et al’s study\textsuperscript{(7)} in this issue provides additional support for the protective effects of polyphenolic antioxidants on CVD. The consumption of fruit-derived polyphenolics in wine or in other forms can change the composition and chemical properties of plasma and its isolated components, making them more resistant to oxidation. The indexes used by Nigdikar et al are common to this burgeoning area of nutrition research, showing that global measures of plasma oxidative susceptibility change with moderate polyphenol consumption. This finding confirms the observations of others on wine (8–10), tea (11), and grape juice (12). Nigdikar et al’s study is particularly important in its efforts to systematically document changes in apparent biological responses resulting from differences of in vitro methods. Specifically, their study explains why de Rijke et al\textsuperscript{(13)} found no change in selected indexes of oxidation whereas Fuhrman et al\textsuperscript{(14)} provided evidence of antioxidant effects in studies of similar design.

Although such inferential indexes certainly show that real changes are taking place with respect to oxidation of plasma components, the mechanism for this effect has not been established, as Nigdikar et al note. The need for mechanistic research is particularly essential for phytochemicals and so-called functional foods, for which commercial interests are at stake and a lack of mechanistic understanding does not preclude investigators from interpreting their observations aggressively. Obviously, the first priority must be to conduct research to develop mechanisms of action that directly relate to healthy physiologic processes, disease development, or both.

The goal of understanding the mechanisms of action of polyphenolic compounds requires concomitant development and validation of unequivocal methods to measure those actions. For example, Nigdikar et al note that several plausible mechanisms could explain the observed increases in plasma oxidative resistance. Phenolic compounds in wine are well-described antioxidants and if absorbed into the blood should cause more resistance to oxidation. Nigdikar et al describe a plasma concentration of phenolic compounds measured with the Folin-Ciocalteau method\textsuperscript{(15)} that is sensitive to nearly all oxidizable compounds. Expanding on Nigdikar et al’s comment that plasma phenolics are not reliably measured with the Folin-Ciocalteau method, the reported concentrations of plasma phenols (22–26 mg/g protein) are equivalent to the concentration in red wine (1.7 g/L) and would be fatal\textsuperscript{(16)}. These concentrations are in stark contrast with those reported by chromatography, typically < 100 ng/L plasma. The need to develop reliable methods to measure individual compounds as well as classes of compounds in body fluids and tissues is apparent and intensive efforts in this direction must be supported.

Nigdikar et al show that not only is the subject’s plasma more resistant to oxidation, but the LDL fraction is also harder to oxidize, again confirming the original report by Fuhrman et al\textsuperscript{(14)}. The mechanism for this effect is unclear because wine phenolics are known to be lost during LDL dialysis\textsuperscript{(17)}. Conjugation between phenolics and LDL particles has been proposed\textsuperscript{(18)} but the chemistry of such a conjugate is obscure.

In addition, although the measured indexes show real changes as a result of polyphenol consumption, these changes have no documented relation with CVD or other disease development. Others have questioned the value of such measurements for clinical evaluation on similar grounds\textsuperscript{(19)}. Decades were needed to establish the correlation between plasma cholesterol concentrations and coronary mortality, yet plasma cholesterol concentra-

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The results of Nigdikar et al’s study show that the consumption of fruit-derived polyphenolics can change the composition and chemical properties of plasma and its isolated components, a fundamental advance in understanding the role of dietary polyphenolics. Whether or how this translates into a net nutritional benefit is an exciting basis for future research that must first uncover more specifics on the mechanisms of how polyphenolics affect health and disease.

REFERENCES