Annu. Rev. Nutr. 2000. 20:561–93

THE HEALTH BENEFITS OF WINE

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Key Words moderate ethanol intakes, polyphenols, chronic disease, oxidation, nutrition

■ **Abstract** Epidemiologic studies from numerous disparate populations reveal that individuals with the habit of daily moderate wine consumption enjoy significant reductions in all-cause and particularly cardiovascular mortality when compared with individuals who abstain or who drink alcohol to excess. Researchers are working to explain this observation in molecular and nutritional terms. Moderate ethanol intake from any type of beverage improves lipoprotein metabolism and lowers cardiovascular mortality risk. The question now is whether wine, particularly red wine with its abundant content of phenolic acids and polyphenols, confers additional health benefits. Discovering the nutritional properties of wine is a challenging task, which requires that the biological actions and bioavailability of the >200 individual phenolic compounds be documented and interpreted within the societal factors that stratify wine consumption and the myriad effects of alcohol alone. Further challenge arises because the health benefits of wine address the prevention of slowly developing diseases for which validated biomarkers are rare. Thus, although the benefits of the polyphenols from fruits and vegetables are increasingly accepted, consensus on wine is developing more slowly. Scientific research has demonstrated that the molecules present in grapes and in wine alter cellular metabolism and signaling, which is consistent mechanistically with reducing arterial disease. Future research must address specific mechanisms both of alcohol and of polyphenolic action and develop biomarkers of their role in disease prevention in individuals.

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INTRODUCTION

Controversy is common during efforts to define the role of nutrition in health, but few modern reflections of such controversy are as vivid as the debate over wine. In 1991, *60 Minutes*, CBS News' popular television news magazine, presented an appealing scientific report called "The French Paradox," which detailed intriguing epidemiological observations made as part of a large epidemiological study that compared dietary intakes and disease incidences in several different countries, including Canada, Italy, France, Britain, and the United States. Known as the MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease), it found that red wine consumption provided an apparent paradoxical protection from atherosclerotic cardiovascular disease in the French population (144). According to the MONICA data on diet and disease, the French population had a lower incidence of atherosclerosis-related deaths than populations from the other countries studied. Low death rates among the French occurred despite the consumption of diets normally linked to high rates of atherosclerotic mortality and blood cholesterol concentrations consistent with elevated atherosclerotic risk. Americans were tantalized by the possibility that, by drinking red wine each day, they, like the French, could eat a diet high in total fat and saturated fat without markedly increasing their risk for death by atherosclerosis. Scientists in California hypothesized that the polyphenols in red wine constituted a source of dietary "antioxidants" that could mitigate atherosclerotic disease development among the French (43, 88). The hypothesis further predicted that these same compounds, as components of fruits and vegetables, could contribute to protection from other oxidant-linked chronic diseases (43, 88). The predictions and provision of several plausible and testable mechanisms for observed epidemiological relationships prompted a large number of researchers to address the issue of the health benefits of wine consumption.

WINE, A NUTRITIONALLY COMPLEX FOOD

Sociological Factors Confound Epidemiological Conclusions

Epidemiological evidence from various populations around the world has consistently identified wine consumption with increased longevity and reduced atherosclerotic mortality (26, 59, 61, 62, 94, 150–153, 178, 194). However, a statistical correlation between wine consumption and lower rates of atherosclerosis does not genuinely resolve the key question of whether it is wine consumption or its associated pattern of moderate ethanol consumption that is associated with decreased atherosclerotic mortality.

The term wine describes a diverse commodity class composed of the yeast fermentation products of the must, or juice, pressed from grapes, the fruit of the genus *Vitis*. Wine is a fruit product, but fermentation produces a variety of chemical changes in the must, and so wine is not simply grape juice with ethanol added. Fermentation alters the must by altering the conjugation of organic acids and phenolics (phenolic acids and polyphenols), by extraction and formation of copigments and the development of an anaerobic and protective redox potential. Wine becomes a unique and highly valuable food product by biotechnological processing of juice that is derived from an intensively cultivated agricultural commodity.

Different grape and wine varieties have emerged over the centuries of cultivation, according to the skills and tastes of grape growers and wine makers. Most of the differences between grape varieties and, hence, wines arise from variations in secondary plant metabolites that significantly influence the taste, flavor, color, and stability of the wine as a beverage (166). Enologists emphasize the differences between wines concerning color, aroma, flavor, and product stability (174); such differences are one basis for wine preferences among consumers and for patterns of spontaneous wine consumption within populations.

Wine, and especially red wine, is a luxury product, usually consumed as part of a full meal, and it is astringent and bitter. As a result, spontaneous wine consumption, within pre-1991 populations particularly, depends on multiple cultural, social, economic, and gender- and age-related factors (31). These complex factors that underlie spontaneous wine consumption make it possible that some other important variable or coincident patterns of behavior that have yet to be statistically isolated and that are highly correlated with wine consumption are truly responsible for increased longevity within wine drinking populations. Indeed, the correlation of wine consumption with other health-promoting dietary factors is highly significant (186). Thus, ecological epidemiology has served as an excellent means to generate hypotheses, but, at the same time, the bias inherent to wine drinking among the populations studied provides this approach with little ability to resolve the health benefits of wine.

Compositional Factors Complicate Experimental Conclusions

Nutritional valuation of wine depends greatly on the determination of whether wine provides benefits that are independent of its association with a pattern of regular moderate ethanol intake (50, 61–63, 89, 90, 110, 135, 150, 187, 194). Red wine constitutes a reliable and rich source of biologically active phytochemicals, specifically phenolic acids and polyphenols, whose individual and summated actions are believed to provide health benefits.

Compositional data on wine are voluminous but unorganized for nutritional purposes, largely owing to the concomitant lack of data on the bioavailability and effects of individual wine components. Moreover, wine chemistry is complex, and it can be expected that considerable time and effort may be expended before the important nutritional variables in wine are fully characterized. Progress toward such determinations will be accelerated by studies that provide as much compositional data as possible for wines used experimentally. Currently, useful minimum information includes estimates of total phenolic acids and polyphenols and provision of variety and vintage (age).

More detailed information on wine composition will facilitate estimates of the availability and metabolism of individual wine components within the body. As such information becomes available, mechanistic studies in model systems must be pursued, using physiologically relevant compounds and concentrations. Detailed databases developed from such efforts will ultimately provide the means to form the generalizations necessary for dietary recommendations concerning wine consumption. Subsequent sections of this review attempt to convey the complexity of wine chemistry and to document what is currently known about the effects of individual wine components, including ethanol, on the major nutritionally responsive chronic diseases. This approach is taken because at present the best definition of health that the literature can support is the absence of disease.

ETHANOL

Wine contains 8%–15% ethanol by weight, and the associations between ethanol consumption and the major nutritionally responsive chronic diseases of atherosclerotic cardiovascular disease, diabetes, and cancer are qualitatively different. The consensus view developed from >50 published epidemiological studies was summarized in a 1999 International Life Sciences Institute Europe monograph (102). This group accepted as scientific fact that the effects of ethanol on overall mortality in modern western populations follow a J-shaped curve. In such a relationship, moderate ethanol intakes produce a significant reduction in mortality relative to abstinence from ethanol, but, beyond moderate intakes, mortality rises sharply. For example, in a prospective study in eastern France, it was concluded that a moderate intake of wine, defined as two to five glasses per day, was associated

with a 24%–31% reduction in all-cause mortality (145). However, in a case-controlled study, immoderate drinking, defined as 1.5 liters of wine/day, nearly trebled the risk of head and neck cancer for individuals who smoked more than one pack of cigarettes per day (1). A 1996 review (65) defined reductions and increases in risk for different diseases in men and women by amounts of ethanol consumed.

Atherosclerotic Cardiovascular Disease

Relationships between atherosclerotic mortality and ethanol intake differ from those of ethanol and other causes of mortality in that immoderate ethanol consumption causes little increase in atherosclerotic mortality (19). The unique relationship between ethanol intake and atherosclerotic mortality is believed to be derived largely from the direct metabolic effects of ethanol on lipoprotein biology. Ethanol causes well-described elevations in plasma high-density lipoprotein (HDL) cholesterol, a protective factor against atherosclerotic cardiovascular disease (23,140, 183, 184). Epidemiological data and the known quantitative relationships between plasma HDL concentrations and protection from atherosclerotic-disease risk were used to estimate that increases in HDL account for approximately half of the overall protection from atherosclerotic disease mortality in populations that consume moderate amounts of ethanol (94). Other mechanisms have been proposed to account for the reported ability of moderate ethanol consumption to reduce cardiovascular disease, including ethanol's mitigating actions towards vascular disease of occlusive and aggregatory origins. Data are currently limited, but suggest that wine is not as protective against incidence of stroke, both ischemic and hemorrhagic, and peripheral hypertension (94, 139).

Ethanol acts to raise HDL cholesterol. To date, no other diet or lifestyle variable influences HDL in such a consistent manner. Moderate ethanol intake appears to be protective in all populations studied, possibly because it has no other variable that is potentially confounding or acts to provide a similar benefit. The nonalcoholic molecules in wine, however, are proposed to be the same as those in many fruits and vegetables (see below). Hence, one would predict a priori that the effects of the nonalcoholic wine molecules would contribute an indiscernible benefit in epidemiological studies within populations that ingest large quantities of fruits and vegetables. Alternatively, in populations that consume relatively few fruits and vegetables, red wine can be the major source of phenolic acids and polyphenols in the diet. In these populations, red wine intake would be a distinctly and significantly different source of ethanol affecting atherosclerotic cardiovascular disease risk. In studies to date, those populations that ingest a Mediterranean-style diet (90) that is rich in fruits and vegetables show the least disparity between forms of ethanol and atherosclerotic cardiovascular disease risk. However, in populations such as were found in Denmark, among whom fruit and vegetable intakes were limited, wine consumption showed a clear benefit over other forms of ethanol (61, 110, 135, 187, 194, 201).

Diabetes

Moderate ethanol intake is not generally contraindicated in diabetes (77). Relatively large doses of ethanol, for example, 1 g/kg[1] body weight given as a 40-ml vodka apéritif, 400 ml of red wine with dinner, and 40 ml of cognac with coffee after dinner, had no effect on the glycemic control of insulin-dependent diabetics (92). This same regimen enhanced meal-induced insulin secretion in noninsulin-dependent diabetics, thus reducing fasting blood glucose concentrations (92). Glucose counter regulation was impaired by ethanol-mediated suppression of lipolysis and plasma free fatty acid concentrations in individuals with insulin-dependent diabetes when they consumed 750 ml of red wine (ethanol = 12% wt/vol) over a 3-h time period (7). Diabetics are at increased risk for atherosclerotic cardiovascular disease (85, 138, 188) and exhibit manifestations of oxidative damage in several ways (141, 142), including formation of glycosylated proteins and lipids (10, 17, 78). Thus diabetics as well as nondiabetics would be expected to benefit from many of the favorable effects of moderate ethanol intake on atherosclerotic cardiovascular disease risk factors and lipoprotein metabolism. Very little information is available on the effects of wine polyphenols on diabetes, although the confounding lifestyle variables associated with spontaneous wine consumption, namely, reduced smoking, increased exercise frequency, and better dietary habits, mimic general recommendations given to diabetics. One study examined the ability of high- or low-flavonol diets to reduce the severity of lymphocyte DNA oxidative damage as assessed by single-cell electrophoresis assay among noninsulin-dependent diabetics (97). High dietary flavonol intakes derived from tea and onions decreased peroxide-induced DNA strand breaks compared with the effects of low flavonoid diets (97).

Cancer

Relationships between moderate ethanol intake and cancer risk are less clear. At high intakes, ethanol is highly associated with increased cancer risk, and alcoholism is a well-established predictor of cancer of the oral cavity, larynx, esophagus, and liver (79) but not the prostate (82). Substantial evidence was presented that consumption of only one or two drinks of ethanol per day increased the risk of breast cancer (100, 101). However, others did not observe this relationship (48, 206). Among subjects participating in the Framingham Study [Framingham, MA (206)], breast cancer was not particularly associated with wine, beer, or spirits consumption when assessed separately, and light consumption of any form of ethanol-containing beverage was not associated with increased breast cancer risk. There was little evidence that linked a lifetime of relatively low ethanol intake and breast cancer risk for any beverage except beer within a group of pre- and postmenopausal women (47). Purohit (137) reviewed the literature to evaluate associations between moderate ethanol consumption and plasma estrogen concentrations in healthy postmenopausal women. Ethanol consumption by women

who were on estrogen replacement therapy appeared to have an increased risk of breast cancer (66). Calabrese (18) and others (51) consider resveratrol in wine to be a phytoestrogen. Resveratrol exhibits physiological effects in vitro, such as an ability to activate estrogen receptors. These investigators proposed that, through this action, moderate red wine consumption could provide some protection against the breast cancer-promoting effects of ethanol.

Ethanol source is often reported to have differential effects on cancer development. Gronbaek et al (60) determined that a moderate intake of wine was unlikely to increase the risk of upper-digestive-tract cancer, whereas a moderate intake of beer or spirits did increase this risk. In yet another study, Prescott et al (135) reported that the risk of lung cancer was associated with a high consumption of beer and spirits, whereas wine may be protective. Occupational exposure to cigarette smoking and consumption of beer, but not wine or spirits, was associated with development of transitional cell carcinoma of the bladder (136). In Uruguay, hard liquor drinking was associated with a higher risk of oral cavity and pharynx cancer than was wine drinking (29). Evident from the studies reviewed above is that the association of ethanol intake with various types of cancer is dependent on both quantity of intake and type of ethanol-containing beverage consumed. Overall, population studies show that moderate consumption of wine ethanol, especially red wine ethanol, is associated with cancer less often than is consumption of similar quantities of other ethanol-containing beverages. However, as with correlates to general increases in longevity, definitive statements about why red wine consumption is less associated with cancer risk than is consumption of other forms of ethanol are compromised by the healthy diet and lifestyle of spontaneous red wine drinkers (186). At present, evidence is nonexperimental, and the opportunities for confounding with other dietary factors are large. In all reports, immoderate ethanol intake increased cancer risk.

Given that only moderate ethanol intakes are associated with increased longevity, it is important to define ethanol in takes that are consistent with moderation. The National Institute on Alcohol Abuse and Alcoholism defined a single moderate serving of wine as 120 ml, providing 12.4 g of ethanol (117). Others defined a serving as 150 ml (127). In >30 studies of populations drawn from around the world, ethanol intakes of 10–40 g/day were associated with significantly lower risk of atherosclerotic cardiovascular disease mortality (discussed above). Currently, there are no reliable biomarkers for moderate ethanol intake, and "moderate daily intake values" rely on self-reported consumption data. The lack of detailed mechanistic understanding of precisely how ethanol exerts its myriad metabolic and physiological effects precludes conclusion or prediction as to even how ethanol would be delivered for optimal effects. For example, if many of the beneficial aspects of ethanol effects result from its properties as a hepatic or peripheral fuel, it may be preferable to deliver ethanol as a nutrient gradually over the entire day. However, if the net beneficial effects are caused by increasing defense mechanisms via a cellular response to stress induced by ethanol, it is possible that the acute dosing through ethanol-containing beverages is superior. Molecular

damage and stress from ethanol intake have been measured. A study conducted under metabolic-ward conditions showed that the oxidative stress indicator isoprostane F2a-III increased after ethanol consumption in a time- and dose-dependent manner in healthy volunteers (109). Ethanol doses of 0.2–0.4 g/kg of body weight did not increase urinary isoprostane F2a-III, but 0.6 g/kg body weight or more did. As a working definition derived from a chemical indicator, this review defines wine intakes of ethanol of $\geq$0.6 g/kg body weight as higher than moderate.

NONALCOHOLIC COMPONENTS

The Molecules in Wine

The composition of wine is summarized in Table 1. As is true of any natural biological material, the composition of all components varies over a significant range (21). The widest and perhaps most important variation is in the composition and content of secondary plant metabolites, collectively termed polyphenols (Table 2). The majority of grape polyphenols are present in the skins and seeds, and, as a result, the processing of grapes into wine has a greater effect on the total polyphenol content than does grape variety, although grape variety and growing conditions influence the spectrum of polyphenols present in the grapes. Skins and stems are left in contact with the must for prolonged periods to produce red wines, whereas stems, skins, and must are rapidly separated after the crush (juice extraction) to make white wine. Aging increases various chemical processes that continue to alter composition (15).

The phenolic acids and polyphenols of grapes appear to be the major components with antioxidant properties. When the ability of different wine varieties to act as antioxidants was tested, antioxidant activity varied with the total phenolic acid and polyphenol content, expressed as gallic acid equivalents (45). From even this simple chemical perspective, red wines vary in total gallic acid equivalents and chemical antioxidant activity by a factor of 4, whereas red and white wines may differ by a factor of 30. Table 2 shows the classes of wine phenolic acids and polyphenols and lists some representative molecules of each class. It becomes obvious that wine is a rich source of a large number of individual phenolic acids and polyphenols. In this regard, wine differs from other well-studied foods, such as onions, that contain predominantly a single flavonoid, the flavonol quercetin, as a variety of glycosides (129). Each phenolic compound present in wine may have individual biological effects that are distinct from a contribution to a general antioxidant capacity as defined by gallic acid equivalents, and this simple fact of wine biology makes many of the fundamental interpretations about the health effects of wine complex.

Previously, there has been little motivation to study wine chemistry systematically from a nutritional perspective, and, to date, only obvious and rudimentary

TABLE 1 Composition of wine excluding phenolic acids and polyphenols

Component	Concentration (g/100 ml)
Water	80–90
Carbohydrates[a]	
Glucose	0.05–0.1
Fructose	0.05–0.1
Pentoses	0.08–0.2
Arabinose, rhamnose, xylose[b]	
Pectin	Trace
Inositol	0.03–0.05
Fucose	0.0005
Alcohols	
Ethyl	8.0–15.0
Other	
Methyl, higher, 2,3-butylene glycol, acetoin[b]	0.3–0.19
Glycerol	0.30–1.40
Aldehyde	0.001–0.050
Organic acid	
Tartaric, lactic, succinic, acetic, *p*-hydroxy-glutaric, galacturonic, amino, malic, citric, fumaric, oxalic, α-ketoglutaric, aconic, citra-malic, malonic, pyrorocemic, pantothenic[b]	0.3–1.10
Nitrogenous compounds	
Amino, ammonia, amide, protein humin[b]	0.01–0.09
Mineral compounds	0.15–0.40
Potassium, magnesium, carbon dioxide, phosphate sulfate, calcium, chloride, silicic acid, fluoride, aluminum, manganese, sodium, iron, boron, iodine, copper, rubidium, oxygen[b]	

[a]Concentration is dependent on style of wine, that is, dry or sweet.

[b]Individual compounds are ranked in decreasing concentrations.

comparisons between red and white wine have been made. Currently, there are inadequate data to suggest that a particular spectrum of phenolic acids or polyphenols will provide an advantage over another mixture to prevent a particular disease or to suit a particular metabolism. Efforts were made to describe "serving equivalents" for several foods based on total polyphenol content (127). Based on the calculations of Panganga et al (127), the antioxidant activity in 1 glass of red wine (150 ml) was equivalent to that found in 12 glasses of white wine, 2 cups of tea, 5 apples, 5 (100-g) portions of onion, 5.5 portions of eggplant, 3.5 glasses of black currant juice, 500 ml of beer, 7 glasses of orange juice, or 20 glasses of apple juice (long-life). Red wine is thus a concentrated source of dietary phenolic acids and polyphenols.

TABLE 2 Phenolic acid and polyphenol components of red and white wines[a]

Component	Concentration (mg/L)	
	Red wine	**White wine**
Nonflavonoids	240–500	160–260
Hydroxybenzoic acids	0–260	0–100
p-Hydroxybenzoic acid	20	—
Gallic acid	116 (26–320)	1.4
Total gallates	40 (30–59)	7 (6.8, 7.0)
Salicylic acid	—	—
Syningic acid	5 (4.2–5.9)	—
Protocatechuric acid	88	—
Hydroxycinnamic acids	162 (62–334)	130–154
cis/trans-Coutaric	20 (16–24)	1.8
cis/trans-Caftaric	25 (11–47)	5 (3, 7)
Caffeic acid[b]	8.5 (3–18)	2.8
Coumaric acid[b]	12.6 (7.5–22)	1.5 (1–2)
Ferulic acid[b]	19	—
Stilbenes	12.3 (4–19)	1.8 (0.04–3.5)
trans-Resveratrol	1.0 (0.1–2.3)	0.22 (0.003–2.0)
Flavonoids	750–1060	25–30
Flavonols	98 (10–203)	Trace
Quercetin	18.8 (5–53)	0
Myricetin	16.2 (2–45)	0
Kamempferol	18	0
Rutin	6.8 (0.5–10.8)	0
Flavanols	168 (48–440)	15–30
Catechin	89 (27–191)	17.3 (3–35)
Epicatechin	57.3 (21.4–128)	13.6 (2, 18.9, 21)
Procyanidins	171 (29–333)	7.1 (5–10)
Anthocyanins	281 (20–500)	0
Delphinidin 3-monoglucoside[c, d]	22	0
Cyanidin 3-monoglucoside[c, d]	20 (2.8, 38)	0
Petunidin 3-monoglucoside[c, d]	18	0
Peonidin 3-monoglucoside[c, d]	32	0
Malvidin 3-monoglucoside[c, d]	93 (24–170)	1
Total phenolic acids and polyphenols	1200 (900–2500)	200 (190–290)

[a]Tabular values are reported as milligrams per liter with values drawn from (45, 54, 56, 96, 103, 107, 125, 154, 160, 171–173, 185). Not all authors reported all compounds or classes of compounds. Mean values were calculated from all available values. The range of contributing values is shown in parentheses, whereas range values separated by a comma are the individual literature values contributing to an average. Values without a range are the sole value found. In some instances, only ranges were reported and are shown without a mean value. Dashes indicate no value found in literature.

[b]Also present as tartrate esters.

[c]Also present as a diester with acetate.

[d]Also present as a diester with *p*-coumarate.

Ingestion, Metabolism, and Pharmacokinetics

A portion of the flavonoid content of wine is in the form of polymers that do not readily break down under physiological conditions (tannins) and that would not be expected to be available for absorption (84). Among the nontannin flavonoids in red wine, about half are present as glycosides and half as aglycones (154). Glucosidic linkages, in particular, enhanced quercetin absorption from onions (74, 76). Previously, only aglycone forms were thought to be absorbed. (+)-Catechin and epicatechin are present in wine exclusively as aglycones, and the glycosidic bonds on other wine flavonoids hydrolyze with age. Wine contains nonflavonoid antioxidant compounds such as phenolic acids, of which cinnamates and gallates are typical. Aged red wines also contain complexes of flavan-3-ols and anthocyanins, termed copigments (15). Copigments may function to stabilize both the flavan-3-ol and anthocyanin contents of older wines. The absorption of only a very few of these compounds has been studied to date, and absorption of even fewer compounds has been studied within a wine matrix.

Despite these limitations, available data show that flavan-3-ols, flavonols, anthocyanins, and nonflavonoid stilbenes that occur in red wine are indeed absorbed. Flavonol absorption has been studied primarily with onions as a dietary source (74, 75), and good reviews are available (73). Epicatechin absorption and metabolism were studied within the context of tea drinking (189) and cocoa ingestion (149). Anthocyanin pigments, which are responsible for the red color of wine, were found in human urine (95) and human plasma (128) after wine consumption. Resveratrol, a nonflavonoid trihydroxystilbene, is quantitatively a relatively minor component of red wine (154) and an even less significant contributor to white wines (56). Methods to measure resveratrol were developed (14, 208) and applied to absorption studies in animal models to correlate plasma concentrations with tissue effects (12). Bertelli et al (13) concluded that long-term wine consumption could increase tissue resveratrol concentrations. However, Soleas et al (175) concluded that tissue resveratrol concentrations after red wine consumption were inadequate to suggest that this single compound was the most important contributor to the physiological effects of red wine.

As ingested, phenolic acids and polyphenols possess multiple hydroxyl groups and are subject to further metabolism by enzymes in intestine, liver, and kidney (64, 131, 134, 195). The predominant end products of this metabolism are *O*-methyl esters and glucuronyl and sulfate conjugates of parent compounds. The responsible enzymes have broad substrate specificity with different affinities for specific compounds (83). In addition, tissue enzyme amounts can become limiting, and, under these conditions, metabolism of individual compounds appears to depend on individual substrate concentrations (207). Flavonoids may travel in the body while bound to plasma proteins (105, 161, 162). Conjugated derivatives of quercetin retained partial antioxidant activity, and combinations of conjugates had additive effects (104). In isolated rat intestine, the metabolism of

flavonoid glycosides to the aglycones and thence to specific glucuronides occurred within the intestinal tissue and depended on the structure of the flavonoid (177).

The effect of ethanol on flavan-3-ol absorption was studied in fasting subjects by using a well-characterized wine source (11, 33) containing 35 mg (+)-catechin/120-ml serving. (+)-Catechin circulated in plasma almost exclusively in conjugate forms. Plasma total (+)-catechin increased rapidly to a peak concentration by 1.44 h postingestion, with a return to near baseline values at 8 h postingestion (11). The peak concentration of (+)-catechin in plasma varied widely among individuals, ranging from 15- to 65-fold over a baseline value of <2 nmol liter^{-1}. It is important that plasma responses in a given individual were nearly identical after ingestion of (+)-catechin in the presence or absence of ethanol. Ethanol did significantly reduce the half-life for elimination ($E_{1/2}$). A more detailed analysis of individual metabolite forms of (+)-catechin that included quantitation of 3′-methyl (+)-catechin forms (33) showed that ethanol did not materially alter the distribution of (+)-catechin among the various forms. In this latter analysis, it could not be determined whether ethanol reduced the $E_{1/2}$ of total (+)-catechins, and ethanol had no effect on the $E_{1/2}$ of methylated (+)-catechin forms. It is interesting that 3′-methyl (+)-catechin never appeared in plasma as a sulfate-only conjugate, suggesting that the order of enzymatic modification may influence net metabolism of flavonoids.

The pharmacokinetic parameters for several flavonoids found in wine are shown in Table 3. At present, the basis for apparent differences in selected parameters is unknown and may be flavonoid (food) source specific or flavonoid class specific. Except for the >20 h $E_{1/2}$ for quercetin, flavonoids were rapidly absorbed and excreted, suggesting that daily consumption would be necessary to sustain elevated plasma levels.

TABLE 3 Pharmacokinetic parameters of wine and food flavonoids[a]

	Quercetin[b]		Epicatechin[c]		Catechin[d]	
Parameter	**Fried onions**	**Apples**	**Cocoa A**	**Cocoa B**	**Wine − ethanol**	**Wine + ethanol**
Dose (mg)	68	98	82	164	35	35
$E_{1/2}$(h)	28	23	1.9	2.3	3.8	3.1
T_{max} (h)	0.7	2.5	2.0	2.6	1.5	1.5
C_{max} (nmol liter^{-1})	740	300	355	675	81	91

[a]Pharmacokinetic parameters apply to amounts consumed in native foodstuffs.

[b]From reference 76, analyzed as a two-compartment model. In an earlier study (75) with fried onions, T_{max} was 2.9 h.

[c]From reference 149. A = 40 g Nestle Noir, B = 80 g Nestle Noir.

[d]From reference 33.

WINE AND CARDIOVASCULAR DISEASE

The strongest positive relationship for wine consumption and health is found in consistent reductions in atherosclerotic cardiovascular disease mortality in wine-drinking populations. Data now make it clear that wine polyphenols act through various mechanisms in addition to chemical antioxidant action to effectively reduce disease-provoking processes and provide protection that is separate from that afforded by moderate ethanol intake. Ongoing research must incorporate recent advances in lipoprotein biology and cell signaling, and consider factors controlling increases in lipoprotein oxidative susceptibility.

Lipoprotein Biology

Lipoproteins are highly specialized transporters of lipids and lipophilic compounds. Intimately involved in energy distribution and exquisitely responsive to diet, the number of and subtle variation in the molecular mechanisms that orchestrate lipid disposition continue to be revealed (156, 181, 182, 205). Triglyceride-rich lipoproteins (TRLs) are secreted predominantly from the intestine and liver and then circulate within the vascular bed, undergoing continuous metabolism and remodeling until they are removed by endocytosis via specific receptors. During their metabolism, TRLs are depleted of triglycerides and become smaller, denser, and richer in cholesterol. In fasting humans, most of the cholesterol in plasma is present as low-density lipoproteins (LDLs), which are terminal metabolic end products of hepatic (ApoB-100) TRL metabolism. Most of the balance of cholesterol circulates as HDLs that arise by secretion from intestine and liver and via metabolism within the plasma compartment. Good evidence supports the interpretation that HDLs are cholesterol transporters that return cholesterol from the peripheral tissues to the liver for disposal as part of a reverse cholesterol transport system (37, 176). The metabolism of TRLs and HDLs is linked by lipoprotein-remodeling processes that occur in the vascular compartment. Thus, as the triglyceride cores of larger-diameter TRLs such as chylomicrons, very low-density lipoproteins, and intermediate-density lipoproteins are hydrolyzed, the resulting excess surface phospholipid and cholesterol are transferred to ApoAI-containing HDLs. Lecithin-cholesterol acyl transferase present on HDLs can act on these lipids to form cholesteryl esters that are carried within the core of HDL or exchanged for triglyceride within TRL by cholesterol ester transfer protein (CETP).

The correlation between plasma total cholesterol and atherosclerotic cardiovascular disease mortality is well described for middle-aged males living in the United States (22). Plasma total cholesterol and atherosclerotic cardiovascular disease mortality have a curvilinear association; that is, a doubling of plasma total cholesterol leads to a quadrupling of risk for atherosclerotic cardiovascular disease mortality. This association is so strong and so well studied and described within the population that the correlation curve has been resolved into segments that are

related to the aggressiveness of therapeutic intervention (22). The predictive value of plasma total cholesterol for atherosclerotic cardiovascular disease mortality has rendered this single measurement the most widely used clinical index for the treatment of atherosclerotic cardiovascular disease. However, the strength of the association does not explain why high concentrations of a normal and presumed necessary lipoprotein class causes disease.

Artery pathology in atherosclerotic cardiovascular disease develops over time and consists of subendothelial lipid deposits, primarily as cholesteryl esters, inflammation, and fibroproliferative response of cells within the vessel wall (99). The endothelial lining of the blood vasculature actively maintains the liquid state of blood (55). Myocardial infarction occurs when the endothelial surface loses its ability to maintain blood in a normal liquid state, resulting in platelet aggregation and thrombus formation. The blood clot associated with thrombus formation leads to vascular occlusion, ischemia, and cardiac myocyte death. The most conspicuous manifestation of atherosclerosis-impaired endothelial function are lipid-laden macrophages or foam cells that form fatty streaks and that, after necrosis, leave cholesterol crystals within the arterial wall. Whereas the source of arterial cholesterol deposits was traced to plasma LDL, neither macrophage nor arterial smooth muscle cells took up native LDL, even when presented with high concentrations of this lipoprotein (57, 197). Thus the mechanism underlying the strong association between elevated plasma LDL cholesterol and cardiovascular mortality remained obscure.

In a seminal observation, Goldstein et al (57) showed that, after chemical modification of LDL to a non-native form, macrophages demonstrated rapid massive lipoprotein particle uptake by a receptor that was ultimately identified as scavenger receptor type A (91). From the efforts of many workers, it was recognized that the most physiologically plausible modification to LDL was oxidative modification of lipid moieties (180). Moreover, endothelial cells themselves were likely responsible for LDL oxidative modification (70), and oxidized lipids, particularly arachidonyl-containing phosphatidyl choline (118), formed in this process caused a variety of effects that accelerated lesion formation. Evidence that antioxidants slowed this process was sufficiently convincing to suggest that the oxidation was a causal mechanism and that antioxidants could present a preventive strategy (142, 169). This fundamental chemical mechanism was the basis for the hypothesis that the protective actions of wine polyphenols against oxidation of LDL were the reason that red wine could be antiatherogenic (43, 88).

Wine influences lipoprotein biology through both its ethanol and polyphenol content. Ethanol consumption stimulates hepatic lipogenesis (170) and increases plasma triglycerides (23, 183). Ethanol also increases the peripheral metabolism of TRL, primarily via an increase in lipoprotein lipase (121, 184). Finally, ApoAI and ApoAII gene transcription have been shown to increase in hepatocytes in response to ethanol (80). This combined stimulation of production and enhanced metabolism of hepatic very low-density lipoproteins, together with increased ApoAI and ApoAII production, have the net effect of increasing the production

of HDL within the vascular compartment. Finally, the plasma clearance of HDL, both ApoAI- and ApoAII-containing particles, is slowed in individuals who consume moderate amounts of ethanol (58). As a consequence of this multifactorial stimulation of HDL, HDL particles of all types appear to increase with moderate alcohol intake.

Hypertriglyceridemia is associated with reduced LDL particle diameter (108). Thus, the triglyceride-raising actions of ethanol are potentially detrimental because, when LDLs are resolved into size subclasses, small, dense LDLs are most closely associated with increased atherosclerotic cardiovascular disease risk (93). LDL particles isolated from chronic heavy ethanol consumers were smaller in diameter, richer in triglyceride, and less able to bind to the LDL receptor on cultured human fibroblasts (72). Changes in LDL composition and size have been attributed to inhibition of CETP by ethanol (67, 71). Changes in LDL physical properties and CETP activity returned toward normal values with ethanol withdrawal. Ethanol withdrawal for 28 days had no effect on plasma total triglycerides, concentrations of triglyceride in mmol per gram ApoB, or LDL particle diameter in normotriglyceridemic men who habitually consume 82 g of ethanol/day, but did significantly improve these same parameters in hypertriglyceridemic men who habitually consume similar amounts of ethanol (8). Thus, endogenous hypertriglyceridemia may be exacerbated by relatively high daily ethanol intakes.

Moderate 40-g doses of ethanol in the form of red wine consumed with an evening meal by healthy nonsmoking, normolipemic middle-aged men transiently increased postprandial triglyceride concentration without changing plasma ApoB or total cholesterol concentrations (190). Similar changes were observed with ethanol in the form of red wine, beer, or spirits and occurred in combination with increases in plasma HDL phospholipid and triglycerides (69). Whereas plasma lecithin-cholesterol acyl transferase activity increased slightly, CETP activity and protein amounts did not. The investigators concluded that increased plasma TRL shifted substrate concentrations for lecithin-cholesterol acyl transferase and CETP, thus increasing lipid transfer reactions that cause HDL triglyceride enrichment. These changes can support HDL synthesis through generation and transfer of surface lipids from TRL as they are metabolized. Ethanol also increases HDL (112, 115) by increasing the production of ApoAI and ApoAII (58, 183).

Wine may also affect HDL functionality through ethanol-independent mechanisms. Platelet-activating factor-acetylhydrolase and paraoxanase, more generally called aryl esterase, are enzymes that circulate in association with HDL and metabolize oxidized lipids to nontoxic products. Indeed, the ability of HDL to prevent endothelium-mediated LDL oxidation depends on the presence of both platelet-activating factor-acetylhydrolase and paraoxanase to metabolize biologically active lipids to inactive derivatives (196). Aviram et al (6) tested quercetin and another flavonoid, glabridin, and showed that they stabilized paraoxanase activity in the presence of oxidized lipids.

Oxidation of Low-Density Lipoprotein

The conditions necessary for the initial oxidation of LDL are believed to arise from retention of LDL or other lipoproteins within the cagelike structures of fibers and fibrils that are secreted by cells of the arterial wall into the subendothelial space (118, 198). Altered endothelial permeability and enhanced retention of circulating LDL are among the very earliest indications of vascular damage. In later stages of atherosclerotic lesion formation, altered endothelial metabolism and function, inflammation, and necrotic changes all stem from the generation of reactive-oxygen species (ROS), lipid peroxides, and resultant protein modifications on a variety of targets. The interrelations between lipoprotein metabolism and oxidative damage greatly expand the number of possible sites and mechanisms through which wine phenolic acids and polyphenols can affect atherosclerotic cardiovascular disease (52, 53). To date, the greatest effort has been directed toward describing the in vitro chemical protection of the lipid moieties of isolated LDL, TRL, or model liposomes from oxidation caused by several different initiating species. The relationships are well understood for parent polyphenols (42). The oxidation of polyunsaturated fatty acids in lipoproteins follows a well-described chemistry in which an initiating free-radical reaction starts an autocatalytic chain reaction. In the absence of redox-scavenging antioxidants, this chain reaction accelerates inexorably, consuming polyunsaturated fatty acids and yielding hydroperoxides.

Wine polyphenols are clearly capable of interrupting or slowing lipid oxidation in vitro and interrupting autocatalytic chain reactions of polyunsaturated lipids chemically by trapping the autocatalytic free radical as a stable phenoxyl radical (42, 52). Many of the compounds in wine are redox active, and many are known to slow lipid oxidation in vitro.

The most important question now is whether wine polyphenols can slow lipid oxidation in vivo when consumed in moderate amounts. One approach to answering this question was to measure the susceptibility of LDL that was isolated from subjects before and after the consumption of wine (44, 87, 113, 167), but results from such studies are highly variable. The approach is currently limited by lipoprotein separation methodologies because phenolic acids and polyphenols are water-soluble and the methods used to isolate LDLs invariably remove soluble plasma constituents (120).

Others have attempted to determine whether wine is capable of improving a parameter termed "the total antioxidant capacity" of blood plasma (20, 28, 147, 148). However, the methods used in these studies were nonspecific in that artificial free-radical donors were added to plasma and the rate of oxidation of a nonphysiologic indicator molecule was then measured. Moreover, the measured values have questionable physiological relevance because the initial oxidation of LDL and other lipoproteins is thought to occur in the subendothelial space under conditions that that are not replicated in isolated blood plasma. Such tests might reflect differences in plasma bathing lipoproteins that are trapped in the subendothelium, and, on this basis, these tests could provide relevant information. However, these techniques

do not resolve which compound(s) is responsible for observed changes and so can serve only as a screening tool to justify more specific measurements. It is also unknown how values measured with these techniques relate to plasma polyphenol concentrations, and, as a result, it is premature to infer absorption information from such techniques. Thus a 10-μmol/liter increase in total antioxidant capacity can not be equated to a 10-μmol/liter increase in plasma (+)-catechin after (+)-catechin ingestion.

A final difficulty with these techniques is that the colorimetric assays attempt to assess the effects of redox antioxidant doses that, if 100% absorbed, 100% retained, and present entirely within the vascular compartment, would increase plasma concentrations of redox active constituents by 1%–3% (169). Thus, even if wine phenolic acids and polyphenols were to increase in plasma, this increase could remain undetected against a high background value for general antioxidant capacity, as well as the daily and individual variability that accompanies clinical specimens. Molar relationships between constituent plasma antioxidants and total antioxidant capacity are poorly understood. It remains unclear how conditions that could only be expected to change plasma total antioxidant concentrations by 1%–3% sometimes produce large increases in total antioxidant capacity. The clinical utility of such tests for any purpose was questioned (200).

Metabolic Basis for Oxidative Susceptibility

Brown & Goldstein (16) reasoned that elevated plasma total or LDL cholesterol reflected impaired lipoprotein metabolism and delayed removal from the blood vasculature. Later, we proposed that intravascular aging of circulating LDL caused by prolonged delays in its clearance was the metabolic explanation for accelerated cardiovascular mortality among individuals with high plasma LDL cholesterol concentrations (193). This hypothesis was tested and confirmed, establishing that prolonged circulation and lipoprotein aging linked high circulating plasma, ApoB cholesterol to increases in the oxidative susceptibility of those lipoproteins (193). Relationships among the various biological and nutritional factors influencing pro- and antioxidant effects were described mathematically, including the prediction of a protective role for antioxidant nutrients (193). Reductions in TRL particle size resulting from prolonged circulation and continued remodeling are consistent with increasing the adherence of LDL to the subendothelium and a greater retention within that compartment (198). Thus small, dense LDLs (23a, 93) are likely a surrogate index for pathologic in TRL metabolism or ApoB cholesterol removal.

Animal studies tested wine polyphenol effects in vivo with several functional endpoints such as arterial lipid deposition (4, 5, 27, 46, 68, 203, 204). ApoE-knockout mice, an accepted model for increased lipoprotein oxidation-dependent atherosclerosis formation, that were fed various forms of grape phenolics (wine, grape juice, or purified phenolics) demonstrated consistent reductions in specific indicators for atherosclerotic cardiovascular disease (68). Plasma LDL isolated

from these mice was less susceptible to oxidation ex vivo and contained lower amounts of lipid peroxides, and aortas from these mice exhibited a 48% reduction in plaque formation. It is important that, although these data did not confirm that wine polyphenols act as direct chemical protectors of LDL, they did show that wine polyphenol consumption altered LDL properties in such a way that they were measurably less susceptible to oxidation and that these changes related to a reduction in plaque formation. Plaque formation was reduced 30%–50% in cholesterol-fed rabbits consuming red wine or red wine solids (27) or fed grape proanthocyanidin (204). (+)-Catechin, the predominant flavan-3-ol in red wine, reduced plaque in an atherosclerotic hamster model when fed in amounts equivalent to the total polyphenols consumed by moderate wine drinkers (203). In total, these data support the fundamental hypothesis that lipoprotein stability in vivo is affected by the consumption of polyphenols and that this protection correlates with reduced atherosclerotic plaque in animals.

Vascular-Wall Biology

Chronic and degenerative diseases such as atherosclerosis are characterized not only by dysfunction of extracellular biological chemistry, but also by important regulatory dysfunction of cells themselves. The artery wall is a multicompartmental tissue containing many different cell types whose ongoing dynamic interactions are key to maintaining normal function within a constantly stressed environment. Atherosclerosis develops as a gradually worsening chronic inflammation of the vascular wall (155, 191) whose constituent cellular elements must respond to inappropriately retained lipoproteins and sequelae of oxidized lipids, proteins, inflammatory macrophages, and, eventually, necrotic debris. Many of the responses to such sequelae are independently deleterious (52). Various nutrients and drugs affect the cellular biology of arterial tissue, and, by their actions on specific structural, biochemical, and signaling pathways, putatively slow the damage and consequences of the atherosclerotic condition [(86); e.g. aspirin, which slows platelet aggregation (34)].

It was hypothesized that phenolic acids and polyphenols could possess the capability to act through a multiplicity of mechanisms in addition to chemical antioxidant protection of lipoproteins (52, 53, 88, 164). The most studied of the hypothesized alternate mechanisms involve cellular signaling pathways. To date, and in addition to antioxidant and metal chelating abilities, polyphenols are known to influence signaling in the endothelial cells lining the artery walls. Phenolic acids and polyphenols can also alter signaling in circulating platelets that are able to aggregate on the endothelium and influence cell biology of endothelial and subendothelial cells. Finally, flavonoids also influence macrophages that arrive in the subendothelium, owing to response to injury.

Cell Signaling Wine phenolic acids and polyphenols affect various properties of endothelial cells, platelets, lymphocytes, macrophages, intestinal cells, and smooth

muscle cells (2, 3, 40, 51, 163, 165), and most studies have implicated changes in cell-signaling mechanisms. These studies performed in vitro provide intriguing results and generate important targets for future research, but caution must be used in extrapolating results of studies on cell signaling in vitro to actions in vivo, especially for polyphenols. Many of the biochemical pathways that are used by cells to produce signals use either redox-active cofactors or free-radical intermediates, or they produce free-radical products as the active signaling molecules. Therefore, compounds such as wine polyphenols that can quench ROS, when added exogenously to isolated cells in vitro, could alter the products of oxidative reactions or change the rate constants of redox-active enzymes and could produce highly significant comparative data. But if these same compounds do not reach the same cells in the same concentrations in vivo, the results in vitro must be considered nonspecific and potentially falsely positive, even though the data are highly significant and the mechanisms of action apparently highly specific. Tests must be performed with the molecules as they exist in vivo and at the concentrations likely to be delivered in response to their consumption in foods or wine. Ideally, the results should then be extended to test the same molecules and mechanisms of action in vivo.

Platelets and Aggregation Ethanol itself produces disparate effects on platelets based on dose and frequency of consumption. Moderate ethanol intakes lower the ability of platelets to aggregate when assayed ex vivo, and cessation of high-ethanol consumption (drying out) is well recognized to produce a hyperaggregatable state of platelets (146, 157). This latter effect is termed platelet rebound. The antiaggregation action of daily ethanol consumption was the mechanism originally proposed to account for unusually low atherosclerotic cardiovascular disease mortality in French populations (144) because fatal myocardial infarctions typically result from thrombotic occlusion of the coronary arteries. A strong case developed that grapes and wine contain compounds that slow the processes of platelet aggregation. The platelets of both dogs and cynomolgus monkeys exhibited significantly reduced ability to aggregate after being fed grape juice, whereas orange and grapefruit juice had no effect (124). Rats fed red wine or red wine phenolics showed increased bleeding time in vivo and in vitro and decreased platelet aggregation, adhesion to collagen, and thrombus weight, again when compared with rats fed either white wine or ethyl alcohol (199). Ruf et al (158) showed that platelet rebound in humans and as reproduced in a rat model was eliminated if the source of ethanol that was withdrawn was red wine. This research group further demonstrated that the phenolics of wine, if added separately as an extract, reversed the ethanol-induced hyper-reactivity of platelets (158). Supporting mechanistic studies were performed largely ex vivo and have not identified an explanation for antiaggregatory effects. Despite lacking a mechanism, it is striking that polyphenols exhibit consistent antiaggregative actions in numerous models (5, 32, 41, 124, 143, 158, 199, 202). The consistency of action provides compelling evidence that the nonalcoholic components of wine exert significant and potentially cardioprotective benefits. However,

platelets from humans in Italy (132) and Canada (126) who consumed red wine or ethanol showed significant but similar reductions in the ability to aggregate, leading the investigators to conclude that ethanol is the most important determinant of these effects. In studies of free-living humans, it is difficult to properly account for the variability of the effects of administered polyphenols on platelets, because human diets vary and intakes of various platelet-inhibiting compounds from other foods could confound the results. In contrast, ethanol is readily studied as an isolated variable in which controls strictly abstain from ethanol ingestion during the period of the study.

Endothelial Cells and Vasodilation Wine as an ethanol-containing beverage is well known to affect blood flow in peripheral vessels. However, ethanol and the phenolics present in red wine appear to exert different effects on blood pressure. Red wine consumption altered endothelial function in humans in vivo (98). Endothelial function, measured as flow-mediated vascular reactivity of the brachial artery, increased in subjects who consume red wine compared with controls. Ethanol-free grape juice exerted similar effects on endothelial function in atherosclerotic humans (179). Consumption of grape juice by angiographically distinguished coronary disease subjects significantly increased a functional measure of vasodilatation (flow-mediated vasodilatation) as shown by high-resolution brachial artery ultrasonography in vivo. In the same study, the ex vivo susceptibility to oxidation of LDLs from these humans was decreased by prior consumption of grape juice. Clearly, the nonalcoholic components of wine have beneficial effects on endothelial function that are independent of the ethanol component. Studies with animal models have also described an alteration in apparent endothelial function solely in response to the polyphenolic components of wine. In the spontaneously hypertensive rat, aortic blood pressure and vessel mechanical properties were improved by consumption of wine polyphenolic extracts (114). It is interesting that, in this study, both apple and tea polyphenols were contrasted with the wine polyphenols, and these other phenolic-rich sources did not elicit significant alterations in either blood pressure or fragility and elasticity of the aorta ex vivo. The compositional basis for the differences between the fruits was not determined. Wine phenolics lowered blood pressure and improved aortic elasticity in stroke-prone, spontaneously hypertensive rats (114) and increased coronary flow velocity reserve in humans with adenosine-induced hyperemia (168).

Studies in isolated tissues and cells to identify the molecules in wine that are responsible for effects on endothelial functions and by what mechanisms they operate remain controversial. Both crude mixtures of wine phenolics and various purified flavonoids modulated the properties of isolated vessels and endothelial cells in culture. Flavonoids found in wine modified the ability of endothelial cells to oxidize lipoproteins (130, 131). In isolated artery segments, vasorelaxation in general was promoted by wine phenolics via an endothelium-NO-derived vasorelaxation (2, 3, 25, 32, 38–40, 81, 165). Wine phenolics also altered endothelial expression of adhesion factors and other functional endpoints, which was

consistent with a role of endothelia in artery disease. For example, in endothelial cells, flavonoids and resveratrol inhibited intercellular adhesion molecule-1 and vascular cell adhesion molecule gene expression (12, 35, 36, 49, 116), wine flavonoids inhibited tissue factor expression (133), and wine phenolics stimulated prostacyclin production (163).

Monocytes/Macrophages Flavonoids affect macrophage biology through several mechanisms, including acute enzyme inhibition and broad and even selective regulation of gene transcription (111, 192). In experiments in which mechanisms for the effects of flavonoids on macrophage cellular properties and activities were pursued, free-radical responsive targets were altered, including NF-κB and heat shock proteins (106). In a variety of studies in vitro, wine phenolics or purified flavonoids found in wine inhibited macrophage-stimulated oxidation of LDL (30; reviewed in 4). However, it is difficult to separate the effects on macrophages from those on the oxidation of the LDL directly. Wine phenolics also inhibited the adherence of macrophages to endothelial cells, although again it is difficult to ascribe the mechanisms of these effects as being unique to the macrophages. In some studies, grape phenolics were fed to animals, and the properties of macrophages that were isolated from these animals were examined. For example, compared with controls, the production of ROS in response to phorbol ester stimulation was attenuated in macrophages that were isolated from the peritoneum of mice fed wine phenolics (9).

In summary, the data support a role for both ethanol and nonalcoholic components of wine in altering cellular regulation from modulation of gene transcription to trapping of active metabolites. These effects are consistent with observations of altered platelet behavior, macrophage functions, and endothelial cells, all associated with the vascular wall function. The observations of altered vascular wall function are consistent with predictions that not only atherosclerotic cardiovascular disease but many other diseases with a vascular component would be affected. The ability of wine components to affect endothelia could address many disparate observations that link moderate wine drinking not only with reduced incidences of disease, including macular degeneration (122) and dementia (123), but directly with increased migraine pain (119).

CONCLUSIONS AND FUTURE DIRECTIONS

Wine has been enjoyed by individuals for centuries, and it is widely viewed as an enhancement to the quality of life. Epidemiological research demonstrates that individuals who choose to drink wine in moderation exhibit improved cardiovascular health and, on average, live longer. Scientific research is now undertaking the challenge of understanding precisely how, in nutritional terms, this improved cardiovascular health and longevity is achieved. Two striking conclusions emerge from the current literature of wine intake and its implications to health. The first

is that the protection provided by moderate wine compares favorably with much more substantial changes in diet and lifestyle. The second is that the amount of ethanol that provides optimal health benefit is very low; ∼1–2 glasses of wine or 10–20 g of actual ethanol per day provides maximal protection. Future research must address the precise means by which such a small consumption of ethanol yields such benefits.

The broad outlines to support the hypothesis that polyphenols from wine or other foods are beneficial dietary components are now in place. To date, however, none of the mechanisms proposed to account for modification of disease risk has been demonstrated rigorously in humans, and significant gaps in information exist. Specifically appropriate biomarkers of mechanistic endpoints must still be developed in conjunction with more detailed information on disease processes and phenolic acid and polyphenol metabolism at the tissue and subcellular levels. The current lack of understanding of the mechanisms by which ethanol and other wine components act precludes most nutritional recommendations regarding wine consumption. For example, it is not known whether the benefit of red wine in particular is caused by the tendency to consume wine with meals and thus coconsume macronutrients and ethanol. Is ethanol protective because of its functions as a fuel or as a source of cellular stress, implicating either multiple small intakes during the day or acute, brief intakes for maximum benefit? Are phenolic acids and polyphenols from wine and other fruits beneficial when intakes of vitamins and minerals are nearer optimum than just marginally adequate; thus is wine beneficial only in a bad diet? None of these answers are known. With the human genome project and molecular biology revolutionizing biological science, wine and health should be a high priority on the list of research subjects for scientists of the new millennium.

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