

**WINE AND HEALTH: A PARADIGM FOR ALCOHOL AND ANTIOXIDANTS**

## VINO I ZDRAVLJE: PARADIGMA ZA ALKOHOL I ANTIOKSIDANSE

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**Summary:** Moderate alcohol consumption has been shown in many epidemiological investigations to prolong overall life expectancy by reducing the risk of certain diseases. Those that account most for this reduction are coronary heart disease and ischemic stroke, both of which are caused by atherosclerotic vascular disease. It has been claimed that these effects are beverage-specific, with red wine being the most potent. This review examines the relative contributions of ethanol and the polyphenolic antioxidants of red wine by considering their potential to inhibit atherogenesis and the mechanisms involved. There is good evidence, both *in vitro* and *in vivo*, that ethanol increases production and circulating levels of HDL-Cholesterol, and reduces clot formation by blocking thrombin activity as well as by inhibition of fibrinolysis. It also prevents migration of smooth-muscle cells to the intimal layer of arteries and reduces the incidence of Type II Diabetes Mellitus, a major risk factor for atherosclerotic disease. Red wine, in addition to ethanol, contains many polyphenolic antioxidants that are also present in fruit and vegetables (such as catechin and quercetin), as well as resveratrol that is almost restricted to grapes and red wine. These polyphenols, especially the last-named, have been shown by *in vitro* experiments to exhibit many potent properties conducive to preventing atherosclerosis. In addition to lowering clot formation, they diminish inflammatory reactions by down-regulating production of eicosanoids and cytokines, they prevent oxidation of LDL, reduce expression of cell-adhesion molecules, and increase NO production. However, investigations in whole animals and human subjects have yielded conflicting results. The above paradox can be explained by studies demonstrating that these

**Kratak sadržaj:** Mnoga epidemiološka istraživanja su pokazala da umereno konzumiranje alkohola produžava očekivani životni vek tako što smanjuje rizik od izvesnih bolesti. Pomenuti smanjeni rizik najvažniji je kod koronarne srčane bolesti i ishemijskog moždanog udara, koje izaziva aterosklerotska vaskularna bolest. Postoje tvrdnje da takvi efekti zavise od vrste pića, kao i da crno vino ima najmoćnije dejstvo. Ovaj pregled ispitaće relativni doprinos etanola i polifenolskih antioksidanata iz crnog vina, razmatrajući njihov potencijal da inhibiraju aterogenezu i njene mehanizme. Postoji valjani dokazi, kako *in vitro* tako i *in vivo*, da etanol povećava produkciju i cirkulišuće nivoje HDL-holesterola i smanjuje formiranje ugrušaka tako što blokira aktivnost trombina i inhibiciju fibrinolize. Na taj način sprečava migraciju glatkih mišićnih ćelija u intimalni sloj arterija i snižava incidencu dijabetesa melitusa tipa 2, kao važnog faktora rizika za aterosklerotsku bolest. Crno vino pored etanola sadrži mnoge polifenolske antioksidante takođe prisutne u voću i povrću (npr. katehin i kvercetin), kao i rezveratrol koji se gotovo isključivo nalazi u grožđu i crnom vinu. U *in vitro* eksperimentima pokazano je da ti polifenoli, naročito rezveratrol, iskazuju moćna svojstva koja omogućavaju sprečavanje ateroskleroze. Pored toga što smanjuju formiranje ugrušaka, oni ublažavaju inflamatorne reakcije regulisanjem produkcije eikozanoida i citokina, sprečavaju oksidaciju LDL, smanjuju ekspresiju molekula ćelijske adhezije i povećavaju produkciju NO. Međutim, istraživanja na životinjama i ljudima dala su protivrečne rezultate. Taj paradoks mogu objasniti studije koje pokazuju da te polifenole, uzete oralno, mukoza tankog creva brzo konjuguje sa glukuronidom i sulfatom pre apsorpcije, posle čega bubrezi

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**Abbreviations:** CHD, coronary heart disease; HDL, high-density lipoprotein; IS, ischemic stroke; LDL, low-density lipoprotein; NIDDM, non-insulin dependent diabetes mellitus; NO, nitric oxide.

polyphenols, when taken orally, are rapidly conjugated with glucuronide and sulfate by the small-intestinal mucosa prior to absorption, following which the deactivated water-soluble conjugates are quickly excreted by the kidney. The free biologically-active parent compounds appear in the circulation in very low concentrations and with a very rapid half-life. Uptake by relevant tissues could not be demonstrated. In line with this evidence, red and white wines have comparable effects when administered to humans that are essentially attributable to their alcohol content alone. These findings suggest that dietary antioxidants may be less effective than previously thought.

**Keywords:** bioavailability, blood coagulation, coronary heart disease, diabetes mellitus, ethanol, fibrinolysis, high-density lipoproteins, ischemic stroke, oxidized low-density lipoproteins, polyphenolic antioxidants, resveratrol, smooth-muscle cells

## Introduction

In the last decade of the last century, a great deal of interest and debate focused on the health benefits of alcohol when consumed in moderation. This notion in turn gave rise to further speculation that some alcoholic beverages are more beneficial than others. Various investigators have proposed that wine is superior to all other forms of alcohol, and some have even suggested that red wine is more potent than white wine. Scientific exploration of these ideas has intensified in the first decade of the present century, and the topic is one that has important implications for human nutrition. Unfortunately, it has also captured the attention of the press whose reports have been as inaccurate as they have been sensational.

The objective of this presentation is to describe and assess the evidence for and against these assertions and to distinguish those statements that we can reasonably regard as true from those that are unlikely to be correct, and those that may be correct but require further proof. We will begin with the impact of moderate alcohol consumption upon health and follow that by considering whether wine has a special role. This second phase will force us to address the relative parts played by the two most important biologically active components of wine: its alcohol and polyphenol contents.

Many claims have been made over the last 30 years that alcohol or wine can lower the incidence of various diseases in human subjects. These include intestinal infections such as dysentery and cholera; macular degeneration of the eye; senile dementia and Alzheimer's disease (1). However, the most fully established benefits of these beverages are seen in coronary heart disease (CHD) and ischemic stroke (IS), and the protective mechanisms involved have been extensively clarified. For these reasons, these

odmah izlučuju deaktivirane konjugate rastvorljive u vodi. Slobodna biološki aktivna izvorna jedinjenja pojavljuju se u cirkulaciji u veoma malim koncentracijama i sa vrlo kratkim poluzivotom a njihovo preuzimanje od strane relevantnih tkiva nije se moglo potvrditi. Iz toga sledi da crna i bela vina imaju slične efekte kod ljudi koji se u osnovi mogu pripisati samom alkoholnom sadržaju. Ovi nalazi ukazuju da su antioksidansi u ishrani možda manje efikasni nego što se ranije verovalo.

**Ključne reči:** biodostupnost, zgrušavanje krvi, koronarna srčana bolest, dijabetes melitus, etanol, fibrinoliza, lipo-proteini velike gustine, ishemijski moždani udar, oksidovani lipoproteini male gustine, polifenolski antioksidanti, rezervacija, glatke mišićne ćelije

two conditions that form part of the spectrum of atherosclerotic vascular disease will be the focus of this review.

## Alcohol and Coronary Heart Disease

The initial evidence linking moderate alcohol consumption with reduced incidence of CHD and IS came from epidemiological surveys. These were performed in many different populations embracing all five continents, and with many different study designs.

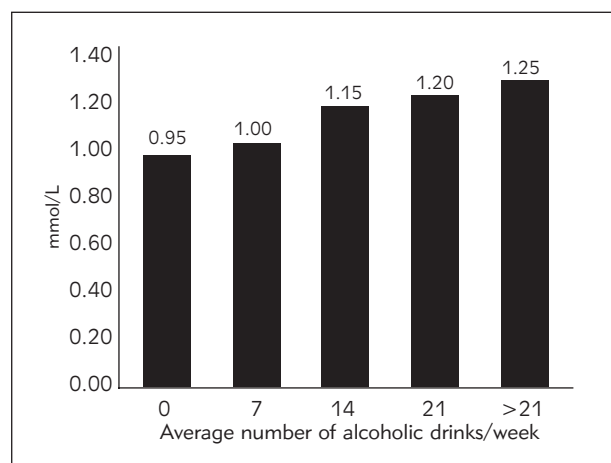
While the results covered a wide span, the rate of CHD in moderate drinkers compared with non-drinkers ranged from 40% to 90%; only rarely did the investigators fail to report a significant reduction. Not only incidence *per se* was reduced by alcohol consumption. This reduction applied to all CHD end-points, including death rate (2), length of hospital stay (3), utilization of health services (4), and *Angina pectoris* (5). Even after myocardial infarction (MI), the risk of a subsequent coronary event was significantly alleviated by moderate alcohol consumption (6). Similar population studies, although on a much smaller scale, revealed that beverage alcohol also lowered the incidence of ischemic stroke (7, 8).

Epidemiological investigations draw our attention to significant associations, but cannot establish a truly causal relationship between the associated phenomena. In the present instance, this requires clear evidence that the factor in question (ethanol) is capable of preventing or reducing the pathological processes that produce the disease. Since both CHD and IS share a common pathogenesis in the form of atherosclerosis and vascular degeneration, it is appropriate to consider whether and how ethanol might affect their development. In fact, a great deal of information derived from *in vitro* experiments as

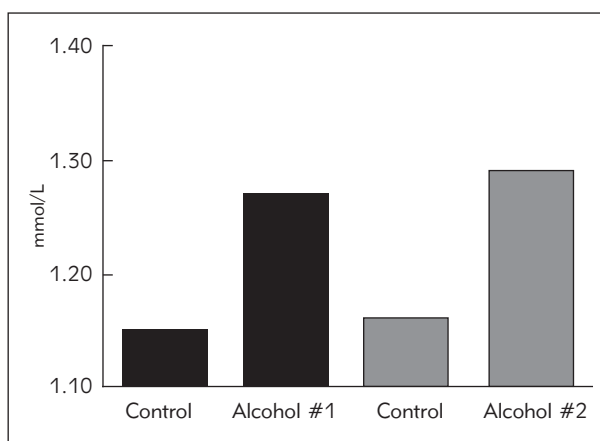
well as *in vivo* investigations showed that ethanol is able to block or significantly reduce many of the key mechanisms that promote the formation of atheroma in arteries. In reviewing this evidence, we will focus upon a few selective mechanisms, all of them of major importance, that happen to be favourably influenced by alcohol consumption. No attempt will be made to comprehensively describe atherosclerosis in mechanistic terms, since excellent publications have already done so (9, 10).

### High-Density Lipoproteins

Deposition of cholesterol within the innermost layer of the arterial wall is a key component of atherosclerosis. Countering this is a process called *reverse cholesterol transport* that removes this cholesterol and transfers it back to the liver. The main agent in this transport is High-Density Lipoprotein (HDL). The higher the plasma HDL, the more cholesterol can be removed from the vessel wall and the lower will be the risk of atherosclerosis. It happens that ethanol is one of the most potent agents that promote HDL production, and this action is its most important contribution to atherosclerosis prevention (11, 12). Epidemiologic studies have shown a steady increase in plasma HDL concentrations with increasing alcohol consumption (Figure 1). More convincingly, when healthy human subjects are switched from 4 weeks of abstinence to 4 weeks of moderate alcohol consumption (13), there is a significant rise in plasma HDL at the end of that period that falls once more when alcohol is withdrawn (Figure 2). Experiments with cultured human liver cells have shown that alcohol acts directly upon these cells to increase their production of the A-lipoproteins that form the structure of the HDL particle (14).



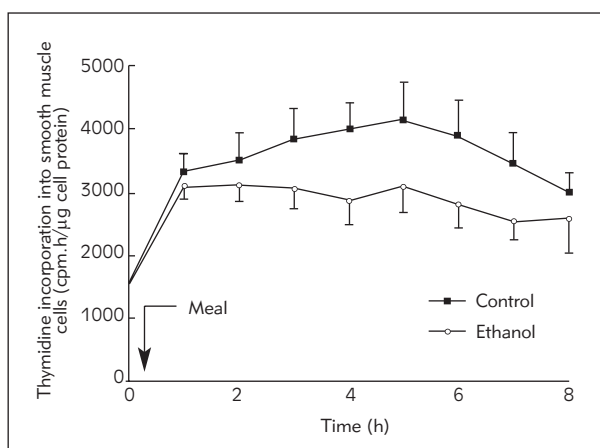
**Figure 1** Epidemiological relationship between weekly alcohol consumption and plasma HDL-cholesterol concentration in human subjects. From Ref. 12, with permission.



**Figure 2** Plasma HDL-cholesterol concentrations, on final day of respective schedule, in 24 healthy males who, in randomly assigned order, drank 375 mL of red or white wine per day for 4-week periods as their sole source of alcohol. During the control periods that randomly preceded or succeeded each wine-consumption period, they avoided alcohol but drank 500 mL/day of commercial grape juice providing equivalent calories. From Ref 13, with permission.

### Smooth-Muscle Cell Migration

A second mechanism of great importance in atherosclerosis is the proliferation of smooth-muscle cells in the medial layer of the artery followed by their migration into the intimal layer. Here they change phenotype to become secretory cells, producing a range of cytokines that contribute to further cellular infiltration of the vessel wall. Analysis of smooth-muscle cells after meals with and without alcohol (15) revealed that its presence reduced proliferation of these cells as measured by thymidine incorporation (Figure 3). It was independently shown that ethanol could reduce their rate of migration *in vitro* (16).

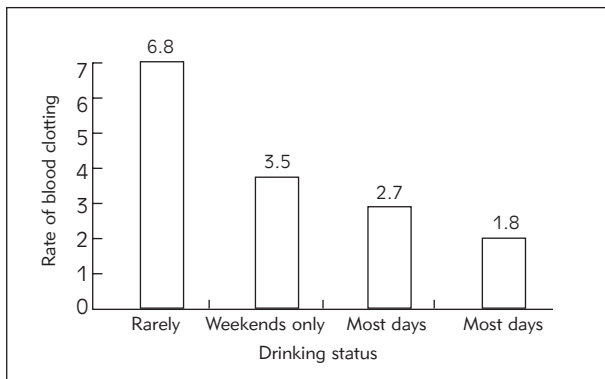


**Figure 3** Time course of smooth muscle cell [<sup>3</sup>H]-thymidine after a fatty meal with and without (control) ethanol (0.5 g/kg body weight) during an 8-hour postprandial period. Data as Mean and SEM (n = 8) are presented as areas under the curve for the corresponding 1-h period. From Ref 15, with permission.

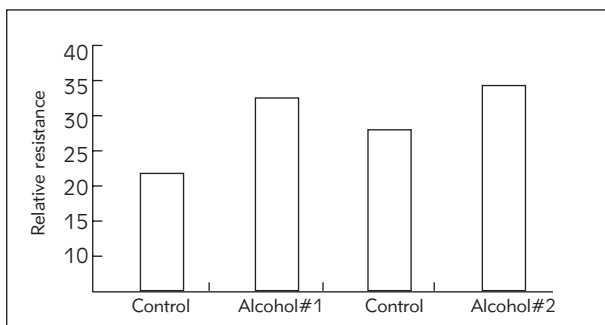
*Blood Coagulation*

Blood platelets have a two-fold role in CHD and IS. They can adhere to damaged vascular epithelium and promote plaque formation by mechanical and secretory mechanisms. They also play a crucial role in the clotting process that is usually the final step in occlusion of an artery already narrowed by atherosclerotic plaque. Both processes are dependent on the »stickiness« of platelets that reflect changes in their membrane structure and phospholipid content, properties that ethanol appears able to modulate (17).

This »stickiness« can be measured by various tests of platelet coagulation in which an agonist (eg. thrombin, collagen, ADP) is used to initiate coagulation, and a dose-response curve is created to calculate the concentration required for half-maximal stimulation (EC50). Epidemiological studies (18, 19) have shown an inverse relationship between alcohol consumption and blood coagulability (Figure 4). Many *in vitro* investigations have revealed a direct inhibitory action of ethanol on platelet aggregation, but most employed much higher concentrations than would be encountered among moderate drinkers

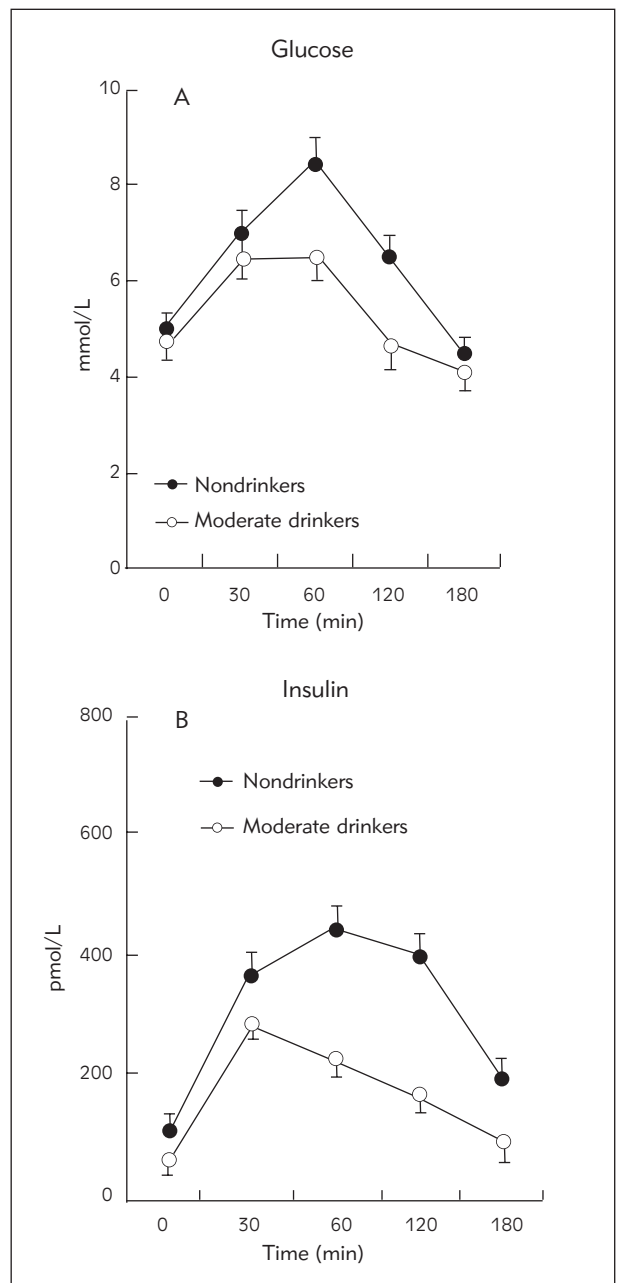


**Figure 4** Epidemiological relationship between frequency of drinking alcohol and relative clotting potential of blood platelets in human subjects. From Ref 18, with permission.



**Figure 5** Relative resistance of blood platelets to clotting measured as the amount of thrombin needed for half-maximal aggregation of washed platelets drawn on the final day of the respective schedule from 24 healthy males under the same experimental protocol described in Figure 2. From Ref 20, with permission.

(17). The issue was settled by a study performed in healthy human subjects who, after 4 weeks of abstinence, were given a moderate amount of alcohol daily for the next 4 weeks (20). Alcohol consumption raised the EC50 for thrombin-induced aggregation which declined when it was withdrawn (Figure 5). Thus, moderate alcohol consumption significantly reduces platelet stickiness and hence their ability to adhere to vascular endothelium and to participate in blood clot formation.



**Figure 6** Response of plasma glucose (top) and insulin (bottom) to an oral glucose load of 75g in 20 non-drinkers and 20 moderate drinkers. Data are Mean and SEM. From Ref 28, with permission.

Alcohol reduces the likelihood and the consequences of blood clotting in at least two other important respects: it lowers the concentration of fibrinogen in the blood (21), and enhances the dissolution of the fibrin clot by promoting the conversion of plasminogen to plasmin, the enzyme responsible for this dissolution (22, 23).

### Risk Factors

So far, we have considered primary mechanisms associated with atherosclerosis, but CHD and IS are diseases in which several known risk factors play important roles. Type II diabetes mellitus (NIDDM) stands out in this respect. In 1982, an epidemiological study reported a lower prevalence of NIDDM in moderate drinkers than abstainers (24). Interestingly, this investigation was based upon a Yugoslavian population and it took 13 years for a group at Harvard University to confirm this observation (25). Since then, reports from many countries (26, 27) have provided further support, and a plausible mechanism to explain these beneficial findings has been revealed. When an oral glucose load was given to non-drinkers and moderate drinkers, the second group responded with a lower increase in blood sugar and insulin concentrations (Figure 6), proving that they had a higher glucose tolerance and greater sensitivity to insulin (28). These features provide strong protection against the development of NIDDM. There is some evidence that two other risk factors for CHD, namely Lp(a) and homocystine, may be reduced by moderate alcohol intake (29, 30), but full confirmation is not yet available.

### Wine and its Polyphenolic Antioxidants

Wine as an alcoholic beverage may be expected to confer all of the health benefits already established for alcohol. In addition to their ethanol content, many wines contain notable concentrations of polyphenolic antioxidants. Most derive from the skin and seeds of the grapes that are removed during white wine fermentation, so that their concentrations in red wine are an order of magnitude greater. The most potent as well as the most extensively studied of these wine polyphenols are catechin, quercetin and resveratrol. By and large, those polyphenols found in wine are also present in fruits and vegetables, often in higher concentrations. The exception is resveratrol that is present in few natural products apart from grape skins and red wine. It also happens to be the most powerful of the wine polyphenols in several *in vitro* tests for properties likely to be helpful in the prevention of atherosclerosis and CHD. For these reasons, it has attracted far more investigative interest than its companions. While the ensuing text will focus on resveratrol, it should be kept in mind that there are several related wine polyphenols that have the same or similar effects to greater or lesser degree.

### Biological Properties of Resveratrol

The biological properties attributed to resveratrol based on *in vitro* experiments are so profuse and diverse, that if they were replicated in whole animals and humans, it would easily qualify as the most powerful molecule in the entire universe. These are summarised in Table I that is by no means complete. Several of these are relevant to CHD prevention and others to cancer prevention (31–33); only the first group will be briefly considered.

Its ability to inhibit thrombus formation, like that of alcohol, involves reduction of platelet »stickiness« and enhancement of fibrinolysis. By down-regulating cyclo-oxygenase activity and eicosanoid production, it will diminish the inflammatory response that is now recognized as a central component in the pathogenesis of atherosclerosis (10). Similar predictions are prompted by its ability to suppress production of a range of pro-inflammatory cytokines. Reduced expression of cell adhesion molecules will limit the entry of monocytes and other cells into the blood-vessel wall where they become transformed into macrophages capable of accumulating large deposits of lipid. Since most of this lipid originates from oxidized-LDL rather than native-LDL (34), the antioxidant

**Table I** Biological actions of resveratrol with implications for disease prevention and improved health. Compiled from Refs. 31–33 where full citations are provided.

<p>PROPERTIES THAT PREVENT ATHEROSCLEROSIS</p> <ol style="list-style-type: none"> <li>1. Inhibition of Inflammatory Processes               <ol style="list-style-type: none"> <li>A) Down-regulates cyclo-oxygenase activity and eicosanoid production</li> <li>B) Suppresses production of pro-inflammatory eicosanoids</li> <li>C) Reduces expression of cell-adhesion molecules</li> </ol> </li> <li>2. Inhibition of Clot Formation               <ol style="list-style-type: none"> <li>A) Lowers platelet stickiness</li> <li>B) Reduces synthesis of pro-coagulatory thromboxanes</li> <li>C) Enhances clot lysis by activating plasmin</li> </ol> </li> <li>3. Anti-oxidant and Free-Radical Scavenger               <p>Prevents LDL oxidation</p> </li> <li>4. Enhances Nitric Oxide Synthesis and Vascular Relaxation</li> </ol>
<p>OTHER PROPERTIES</p> <ol style="list-style-type: none"> <li>1. Inhibits Cancer Initiation and Growth               <ol style="list-style-type: none"> <li>A) Possesses potent anti-mutagenic activity</li> <li>B) Induces apoptosis</li> <li>C) Modulates cell cycle</li> <li>D) Blocks microsomal conversion of aryl-hydrocarbons to carcinogens</li> <li>E) Demonstrates estrogenic activity</li> <li>F) Prevents angiogenesis in cancer tissues</li> </ol> </li> <li>2) Possible anti-viral effects</li> <li>3) May delay ageing processes by modulating sirtuins</li> </ol>

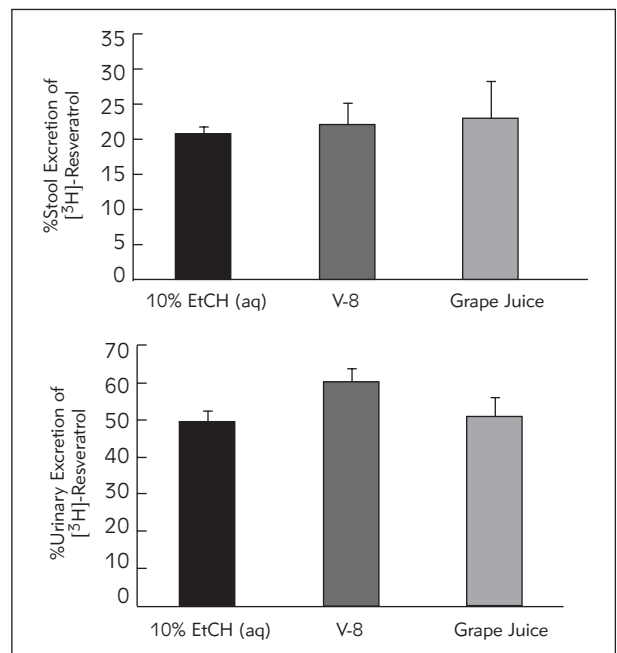
function of resveratrol will help to limit this process. Finally, the benefits of nitric oxide formation and vascular relaxation are self-evident.

#### Absorption and Bioavailability of Resveratrol

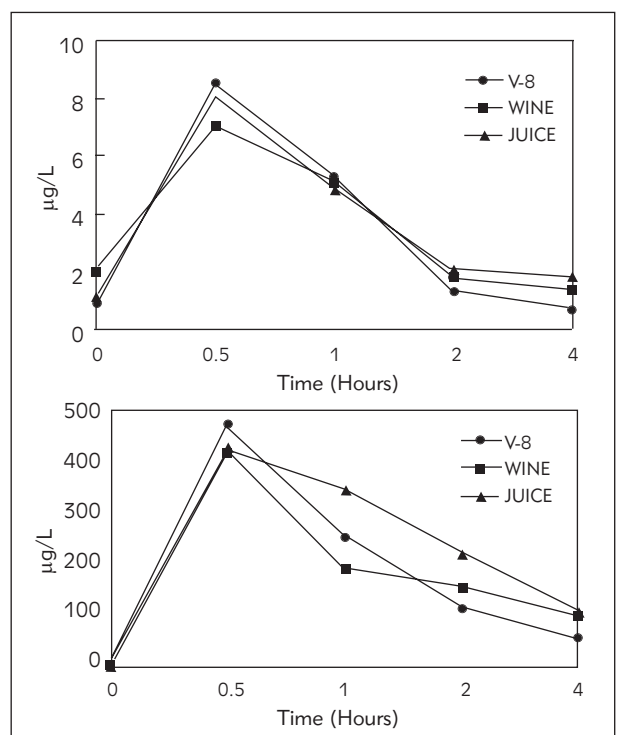
One dilemma remains: all of these wondrous actions require the absorption of resveratrol in adequate concentrations and in an active form. Initial reports of investigations in rats given resveratrol by ingestion of red wine by gavage yielded inconsistent data for the various pharmacokinetic parameters measured (35–37). Peak serum concentrations were reported to occur at 60 min by the first group and at 15 min by the second. Juan and colleagues stated that the peak approximated 10% of the dose given (37), but the peak concentration detected by Bertelli et al. (36) represented only 0.058% of the dose, a concentration more in line with the majority of investigators then and since, and well below that required for significant biological activity of resveratrol based upon *in vitro* results.

Initial approaches to this problem involved administration of tritiated resveratrol to rats in different matrices by stomach tube and following the distribution of the label in animals sacrificed 24-h later (38). Total recovery was in the 70–80% range, with urine and bladder accounting for around 55%, and stool and colon contents for around 20% (Figure 7). Only traces were detectable in the blood (cells and plasma), or in organs such as liver, spleen and kidney. The higher absorption in the vegetable juice matrix argued against competition by other polyphenols in which this juice is enriched. The results favoured very rapid absorption of resveratrol, probably by bulk fluid transfer, with rapid excretion and virtually no tissue uptake or storage.

In subsequent experiments, natural resveratrol was fed to human subjects and its concentration was measured in the blood over the first 4 h and in the urine over the first 24-h (39). *Ex vivo* experiments utilising isolated perfused intestinal loops had earlier shown that resveratrol could be conjugated with glucuronic acid in the rat by enzymes on the mucosal side and transferred as such to the serosal side (40, 41). At the same time, enzymatic sulfation of resveratrol was demonstrated by extracts of human intestinal mucosa (42). We therefore analysed all samples for resveratrol conjugates (sum of glucuronides and sulfates) as well as the free stilbene, using methods specially developed for this purpose (43). The sum of the conjugated and free resveratrol will be referred to as the »Total«. Highest resveratrol concentrations were observed 30 min after consumption, falling to around 20% of the peak by 4 h (Figure 8). Most striking was the finding that at all time points, free resveratrol was only around 2% of the total. A similar situation was observed in urine, where in the first 24 h the total excretion accounted for around 17% of the resveratrol ingested (Table II).



**Figure 7** Recovery of [ $^3\text{H}$ ]-label as percentage of dose given in the rat: (top) stool fraction (colon plus colon contents plus feces) and (bottom) urine fraction (bladder plus contents plus excreted urine) 24-h after intra-gastric administration of [ $^3\text{H}$ ]-labelled *trans*-resveratrol in three different liquid matrices (10% aqueous ethanol; V-8; grape juice). Data are Mean and SEM;  $n=8$ . From Ref 38, with permission.



**Figure 8** Mean *trans*-resveratrol in serum of four subjects given 25 mg of *trans*-resveratrol in three different matrices (V-8, vegetable juice; white wine; grape juice). Top, free resveratrol; bottom, total resveratrol (free plus conjugated). From Ref 39, with permission.

### Absorption and Bioavailability of Other Polyphenols

These experiments were performed using the two other most potent polyphenols present in wine, catechin and quercetin. An identical protocol was used, and the conjugated as well as the free compounds were measured in the serum and urine samples. The results mimicked those obtained for resveratrol in the sense that the conjugates accounted for most of the total content of both polyphenols. The free compound approximated 7.5% of the total in the case of catechin and 20.5% for quercetin. The total urinary recovery of each proved to be a much smaller percentage of the dose ingested than was the case with resveratrol (Table II), averaging 2.2% for catechin and 4.5% for quercetin.

**Table II** Absorption and bioavailability of three polyphenols administered orally to healthy human subjects. Compiled from data in Ref. 39.

	Resveratrol	Catechin	Quercetin
	Mean of 12 Subjects (SD)		
Urinary excretion 24-h after ingestion (% of dose)	16.6 (2.6)	2.2 (0.4)	4.5 (0.7)
Free polyphenol as % of total serum concentration at peak level	1.8 (0.4)	7.5 (1.7)	20.5 (3.3)

These results as a whole point to the following scenario:

1. Most of the resveratrol ingested is conjugated in the intestinal mucosa prior to absorption, with very little of the free compound entering the blood.
2. These conjugates are water-soluble and rapidly cleared from the blood, mainly by urinary excretion.
3. It is unlikely that they are biologically active, since the purpose of conjugation is specifically to inactivate compounds such as drugs and hormones.
4. Its apparently low bioavailability and the low peak concentration of the free compound suggest that circulating and tissue concentrations will not approach those required for meaningful biological activity.
5. It appears that, unlike fat-soluble vitamins, tissue storage of resveratrol does not occur.
6. The above statements apply with equal force to at least two other potent polyphenolic antioxidants that share many of the other *in vitro* anti-atherogenic properties of resveratrol.

Further proof that these polyphenols when collectively present in wine and consumed by human subjects fail to exhibit the beneficial behaviour that they demonstrate *in vitro* was obtained by cross-over studies in which white wine low in polyphenols and red wine high in these constituents were administered to volunteers for 4-week periods following a similar period of abstinence (13, 20). Multiple tests for indices of lipid and eicosanoid metabolism and platelet coagulation performed at the end of each period revealed that both wines modulated those parameters known to be influenced by alcohol, but there was no significant difference between the two wines. Moreover, no additional changes beyond those attributable to alcohol were observed.

### Conclusions

In the decade that has passed since the earlier work described above, the beneficial effects of moderate alcohol consumption upon health, especially in reducing the risk for CHD and IH, as well as the major mechanisms responsible for these benefits, have been repeatedly confirmed (44–50). Interest in the biological actions and potential health benefits of resveratrol have accelerated, and reports have claimed to reproduce several of these in whole animal or human investigations. Paradoxically, virtually all subsequent studies into its bioavailability (51–54) have confirmed its intestinal conjugation, rapid excretion, short half-life, and the ineffective plasma concentrations of the active parent compound, after oral ingestion. The situation is less clear-cut with catechin and quercetin that, in wine, but to a greater extent in beverages (such as tea) and vegetables (such as onions), are present in significant concentrations as condensed polyphenols (anthocyanins and procyanidins) and glycosides whose biological activities are not well defined, and whose absorption and metabolism are likely to be complex. The few reports published in the last several years on the bioavailability of the free parent compounds are essentially consistent with the data presented in Table II above (55–59).

We have been forced to conclude that the polyphenols present in red wine add little if anything to the health benefits conferred by the alcohol that they contain. It has been widely claimed that the presence of these same or similar polyphenols in fruits and vegetables accounts for the highly regarded nutritional value of these foods. It follows from the work described here, and from subsequent reports establishing conjugation of dietary polyphenols in the human intestine as a general phenomenon, that these claims, mostly based on *in vitro* experiments, require serious and critical examination. Until such time as their bioavailability has been proven to generate biologically active concentrations in the circulation and tissues of human subjects, belief in the

antioxidant paradigm should be suspended. It should be recalled that two decades ago, other dietary antioxidants, Vitamins A and E, were recommended for the prevention of CHD but were subsequently shown to be ineffective (60–64). It will be unfortunate if the same fate awaits the polyphenolic antioxidants.

The consolation is that, so far, the benefits of moderate alcohol consumption have withstood scientific challenge, and can be recommended with few restrictions. There is no persuasive evidence that wine offers any special bonus for health, and many authorities now believe that, like those who consume larger amounts of fruits and vegetables, wine-drinkers

are more health conscious, better educated and earn higher incomes than those whose preference lies with beer or spirits (65, 66). Nevertheless, its historical association with food suggests that wine may be the preferred alcoholic beverage in a physiological context.

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### Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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