Effects of red and white wine on endothelium-dependent vasorelaxation of rat aorta and human coronary arteries

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Flesch, Markus, Andreas Schwarz, and Michael Böhm. Effects of red and white wine on endothelium-dependent vasorelaxation of rat aorta and human coronary arteries. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1183–H1190, 1998.—Beneficial effects of wine on myocardial infarction mortality may be because of its vasodilatory properties. This study investigated whether the vasodilatory activity involves the endothelium and is specific for certain wines. Effects of different red and white wines and phenolic grape ingredients on vascular tension and cGMP content were studied in human coronary arteries and rat aortic rings in vitro. Only French and Italian red wines produced “en barrique” (Bordeaux, Châteauneuf du Pape, Barolo) (1:1,000, vol/vol), quercetin (1–100 µM), and tannic acid (1–100 µg/ml) decreased tension of precontracted vascular rings and increased vascular cGMP content (both P < 0.001). The effects were abolished after endothelial denudation and reversible by nitric oxide synthase inhibition. Red wines not produced “en barrique” (Valpolicella, Ahr Spätburgunder), white wines (en barrique-produced Rioja, Chardonnay, Mosel-Riesling), and ethanol did not affect vascular tension or cGMP content. Thus endothelium-dependent vasodilatory effects appear to be specific for red barrique wines, possibly because of their high content of phenolic substances. Divergent effects of wines indicate that a general view on the effects of wine and alcoholic beverages is not warranted.

myocardial infarction; coronary artery disease; wine consumption; quercetin; tannic acid

CORONARY HEART DISEASE is the most significant cause of death in the industrialized countries (24). The search for potential factors influencing the development and the course of the disease have therefore been of great interest during the last decades. Since the early 1970s, there has been increasing evidence that the consumption of moderate amounts of alcohol is inversely correlated with the mortality of myocardial infarction (15, 21–23, 30, 34). The mortality due to myocardial infarction is lowest at a moderate alcohol consumption of 2–3 glasses or 40 ml per day (9, 33). At higher alcohol intake, the risk of sudden cardiac death increases, and overall mortality increases because of an increased incidence of cirrhosis of the liver and cancer (21).

There is some evidence that the protective effects of wine might be more pronounced than those of other alcoholic beverages. St. Leger et al. (36) were the first to demonstrate a strong negative relationship between wine consumption and mortality from ischemic heart disease based on ecological data from 18 developed countries. There was only a weak relationship between the consumption of beer or spirits and the mortality of coronary heart disease. Their findings were later confirmed by an analysis by La Porte et al. (25) and by Criqui and Ringel (7). Interestingly, Renaud and De Lorgeril (29) demonstrated that despite a similar distribution of other coronary risk factors such as high blood pressure, serum cholesterol, body mass index, and cigarette smoking, the mortality of coronary heart disease in France and Switzerland was lower compared with that in other industrialized countries. By analyzing World Health Organization data (40), they (29) observed that this phenomenon might be because of the frequent consumption of wine in France and Switzerland in addition to the potentially important effects of a Mediterranean-style diet. In agreement, Hegstedt and Ausman (20) reported that consumption of wine, but not of beer or spirits, lowered the mortality of coronary heart disease. However, in this study, the predictive value of total alcohol consumption was nearly identical to that of wine. These findings have created some doubts on an exclusive role of wine in the protective effects of alcoholic beverages. These doubts have been confirmed by case cohort studies that did not demonstrate an exclusive protective role of wine (31). There is also evidence for several mechanisms by which the protective effects of wine, but possibly also of alcohol, could be explained. 1) Alcohol consumption leads to a relative increase in the serum levels of high-density lipoprotein cholesterol (4, 17). 2) Alcohol and especially wine have been demonstrated to reduce platelet aggregability, but this effect was achieved in many studies only at very high levels of alcohol with a blood concentration of 0.2 mg/dl and greater (8, 19, 28). 3) A unique benefit of wine consumption could be because of the antioxidative effects of its phenolic components (14, 21). 4) Recently, vasodilatory effects of wine, grape skin extracts, and the wine components tannic acid and quercetin have been described (10). Obviously, “wine” contains a wide spectrum of different ingredients made from different types of grapes grown in different regions and cultivated in very different manners. Thus there might be differences between certain wines, such as between red and white wine and between wines from California, Piedmont, or the river Rhine. Obviously, the sort of grapes primarily used for the wine might be important, such as Cabernet Sauvignon or Merlot in Bordeaux, Grenache and Syrah in Châteauneuf-du-Pape, or the Nebbiolo in Barolo. Finally, pharmacological properties of wine might be influenced by the way the wine is produced, e.g., “en barrique,” in which the wine matures in new oak barrels in contrast to wine production in steel tanks. These differences could be relevant when general conclusions are drawn from correlations of the total amounts of consumed wine in a population to the prevalence of coronary heart disease and to the mortality of myocardial infarction. Therefore, the present study addressed the question of whether there are...
differences between different red and white wines and between wines produced in different ways. The effects of wines and wine ingredients on endothelium-dependent vasodilatation were studied herein as one potentially important mechanism involved in the protective effects in humans.

METHODS

Wines tested in this study. This study aimed to investigate whether there are differences between different wines concerning their vasodilatory effects. Therefore, red and white wines from different areas were compared. In addition, the effects of wine production en barrique by pressing the grapes together with the grape stems and maturation of the wine in oak barrels and the effects of wine maturation in steel tanks were studied.

Red wines studied were as follows: Bordeaux (Château Bilot, Fournier-Casteja, Bégué, Premières Côtes de Bordeaux, France, 1992) and Châteauneuf du Pape (Vignobles Jérôme Quiot, Châteauneuf du Pape, France, 1992) as French red wines produced en barrique; Barolo (Terre del Barolo, Castiglione Falletto, Italy, 1991) as Italian wine produced en barrique; Beaujolais Primeur (Jean Demont, France, 1992) as an example of French red wine that matures in steel tanks but that is pressed and fermented together with the grape stems; Valpolicella (Cantina Del Roseto, Valpolicella, Italy, 1993) as Italian wine produced in steel barrels; and Ahr-Spatburgunder (Ahrweiler Klosterberg, Ahrweiler Winzerverein, Ahrweiler, Germany, 1992) as a German red wine. For the production of this wine, the grapes (grape skins and seeds) are pressed in absence of the grape stems, and the wine matures in steel tanks.

White wines studied were as follows: Rioja (Conde de Valdemar, Martinez Bujanda, Oyon, Spain, 1990) as an example of a white wine produced en barrique; Chardonnay (Freemark Abbey, Napa Valley, CA, 1988) as a California white wine produced in steel tanks; and Mosel-Riesling (Carl Reh, Leiwen, Germany, 1993) as a German white wine produced in steel tanks.

Isolated vessel preparations. Human coronary arteries were obtained during cardiac transplantation from patients suffering from end-stage heart failure (New York Association class IV) due to idiopathic dilated cardiomyopathy. Patients gave written informed consent before the operation. Preoperative treatment of the organ recipients consisted of diuretics, cardiac glycosides, angiotensin-converting inhibitors, and nitrates. General anesthesia was performed with flunitrazepam, fentanyl, and pancuronium bromide with isoflurane. Cardiac surgery was performed while the patient was on cardiopulmonary bypass. After excision, hearts were suspended in ice-cold cardioplegic solution (modified Bretschneider solution; the same as used for the transport of donor hearts) containing (in mM) 15 NaCl, 10 KCl, 4 MgCl\(_2\), 180 histidine HCl, 2 tryptophan, 30 mannitol, and 1 potassium dihydrogen oxoglutarate, pH 7.4, and were delivered immediately from the operation theater to the laboratory. Coronary arteries were prepared under ice-cold cardioplegic solution and transferred in ice-cold modified Krebs-Henseleit solution (in mM: 2.5 CaCl\(_2\), 0.026 EDTA, 11.1 glucose, 4.7 KCl, 1.2 KH\(_2\)PO\(_4\), 1.2 MgSO\(_4\), 118.0 NaCl, and 25.0 NaHCO\(_3\)) aerated with 95% CO\(_2\)-5% O\(_2\). After removal of adventitial and coronary artery rings of 2–3 mm in diameter were prepared using a scalpel and transferred into the organ baths. In some specimens, the endothelium was destroyed by lowering the aortic rings for 3 s into 10% Triton X-100 (26). For preparation of rat aortic rings, male Sprague-Dawley rats (250–250 g) were killed by cervical dislocation. After we removed the heart and lungs, the aorta was prepared from the aortic arch down to the diaphragm and suspended in ice-cold modified Krebs-Henseleit solution preaerated with 95% O\(_2\)-5% CO\(_2\). Preparation was performed within 60 s to prevent blood clotting within the aortic lumen. Adjacent connective tissue was excised, and vessels were cut in rings of 2–3 mm in length. Also, in some rat aortic rings, endothelium was destroyed by lowering the aortic rings for 3 s into Triton X-100.

Determination of the effect of wine and wine components on vascular tension. Contraction and relaxation of isolated vascular preparations were measured in an organ bath containing modified Krebs-Henseleit solution aerated with 95% CO\(_2\)-5% O\(_2\). The temperature was 37°C. Contraction was measured via an inductive force transducer (Föhr Medical Instruments, Egelsbach, Germany) that was attached via an enhancer (Hellige, Freiburg, Germany) to a Gould recorder (Gould, Cleveland, OH). After equilibration for 30 min, the vascular rings were stretched to 10 mN basal tension. This basal tension was kept constant throughout the experiment. Human coronary artery rings were precontracted three times by addition of 100 mM KCl into the organ bath. After each contraction, preparations were washed in bathing solution. To exclude influences of thromboxane A\(_2\) and prostacyclin, experiments were performed in the presence of 10 µM indoethacin. Integrity of the endothelium of the coronary artery rings was tested with substance P (0.1 µM), and integrity of the endothelium of the rat aortic rings was tested with carbachol (3 µM). In vessel preparations in which the endothelium had been destroyed by Triton X-100 treatment, endothelium-dependent relaxation by substance P or by carbachol was abolished, whereas the relaxant effects of sodium nitroprusside were unchanged (data not shown). After precontraction of the vascular rings in response to 1 µM phenylephrine, the effects of wines, quercetin, and tannic acid on vascular tone were studied. The concentration of the wines in the organ bath was 1:1,000 (vol/vol) and thus was within the concentration range that might be obtained in vivo after moderate wine consumption. The effects of the isolated key substances quercetin and tannic acid were tested by cumulative addition of these substances into the organ bath. The effect of ethanol, in a similar concentration as in the examined wines, on endothelium-dependent regulation of vascular tone was determined as control.

Determination of vascular cGMP content. Determination of vascular cGMP content was performed using a commercially available radioimmunoassay (Amersham, Braunschweig, Germany). Immediately after exposure to distinct wines or to quercetin and tannic acid, vascular rings were frozen under liquid nitrogen and stored at −80°C. In the presence of the phosphodiesterase inhibitor IBMX (300 µM), tissue specimens were homogenized mechanically. cGMP was extracted from the pulverized vessel homogenate in 50 µl of 0.3 M TCA and 10 µM HCl per milligram homogenate, and the suspension was centrifuged at 2,000 g for 15 min at 4°C. The protein pellet was stored at −80°C until protein content was determined using the method described by Bradford (3). For extraction of TCA, the supernatant was mixed with the fivefold volume of diethyl ether, the mixture was centrifuged again, and the upper TCA-containing phase was discarded. The procedure was repeated five times, and the remaining diethyl ether was removed from the solution by heating for 5 min at 56°C. The remaining fluid (probes) was lyophilized before determination of cGMP content by radioimmunoassay according to the manufacturer’s instructions.
Materials. Phenylephrine was obtained from SERVA (Heidelberg, Germany). Carbachol was from Merck (Darmstadt, Germany). The cGMP radioimmunoassay was from Amersham (Braunschweig, Germany). All other substances were from Sigma-Aldrich (Deisenhofen, Germany) or Merck. All chemicals were of analytic grade or the best grade commercially available. Only deionized and double-distilled water were used throughout.

Statistics. Data shown are means ± SE. Statistical significance was estimated with Student’s t-test for unpaired observations and ANOVA according to Wallenstein and Fisher (38). A value of P < 0.05 was considered significant.

RESULTS

Effects of different red and white wines on vascular tension. To examine whether the previously described vasodilatory effect (10) is a general characteristic of all wines or is a special characteristic of only some distinct wines, different wines at a concentration of 1:1,000 (vol/vol) were added to the organ bath solution after precontraction of rat aortic rings with phenylephrine. The chosen Châteauneuf du Pape, Bordeaux, and Barolo, thus the three wines produced en barrique, caused a strong vasorelaxation (Fig. 1). This effect was attenuated by addition of nitric oxide (NO) synthase inhibitor N\textsubscript{G}-monomethyl-L-arginine (l-NMMA, 100 µM) into the organ bath (Fig. 1), which indicates that the vasodilatory effect of these wines might be mediated by release of NO. Also, the effect was dependent on the integrity of the endothelium (data not shown). In contrast, the red wines Ahr-Spätburgunder and Valpolicella (matured in steel tanks) had no effect on vascular tone (Fig. 1). None of the white wines tested (en barrique-produced Rioja, Mosel-Riesling, and Chardonnay) induced any relaxation in the isolated aortic rings. In contrast, Mosel-Riesling and white Rioja even caused a minor further contraction. Interestingly, the Beaujolais Primeur (matured in steel tanks but pressed and fermented in the presence of the grape skins and grape stems) also had a significant vasodilatory effect, but this effect was less pronounced than the vasodilatory effect of the red wines produced en barrique. The data of 3–14 individual experiments per wine are summarized in the bar graph in Fig. 2.

To elucidate whether the vasodilatory effect of the red wines produced en barrique might be because of their high content of phenolic substances or tannins, the effects of two commercially available key substances, quercetin and tannic acid, on rat aortic rings and human coronary artery rings were examined. In rat aortic rings, both substances caused a concentration-dependent vasorelaxation (Fig. 4). The effect of quercetin was independent of whether the endothelium was intact or had been destroyed by dipping the vessel ring into Triton X-100 (Fig. 4B). In contrast, the effect of tannic acid was dependent on the integrity of the endothelium (Figs. 4A and 5). Also, addition of l-NMMA (100 µM) attenuated the vasodilatory effect of tannic acid, but not of quercetin (data not shown). These observations indicate that only the effect of tannic acid but not of quercetin is endothelium-dependent and mediated by the release of NO. As can be seen in Fig. 6, effects were identical in human coronary artery rings. Again, tannic acid caused a pronounced relaxation of precontracted coronary artery rings, which
was dependent on the integrity of the vascular endothelium.

Ethanol at a similar concentration as in red wine and as used as solvent for quercetin had no effect on vascular tension (data not shown). Thus the observed vasorelaxing effects are not due to the alcohol content of the examined wines.

Effect of wine components and red wine on vascular cGMP content. Also, to determine whether the endothelial-dependent effects of wine and wine components on vascular tension might be mediated via the NO-cGMP signal transduction pathway, the cGMP content of the vascular preparations was determined after exposure to tannic acid, quercetin, and Châteauneuf du Pape in the absence and presence of L-NMMA and with intact or denuded endothelium. Stimulation of the aortic rings with tannic acid and Châteauneuf du Pape but also with quercetin led to a 4- to 10-fold increase in the vascular cGMP content, the increase being most pronounced after addition of the red barrique wine into the organ bath. Addition of L-NMMA (100 µM) abolished the increase in the vascular cGMP content, as did denudation of the vascular endothelium. This also held true for the effect of quercetin on vascular cGMP content (Fig. 6).

DISCUSSION

Over the last 20 years, there has been increasing evidence that the moderate consumption of alcohol and especially of wine leads to a decrease in the mortality of myocardial infarction. Recently, Fitzpatrick et al. (10) suggested that special cardioprotective effects of wine might partly be due to the vasodilatory effects of its phenolic components and of tannic acid.

In the present study, the question was addressed whether this vasodilatory effect is a general characteristic of wine or whether it is a characteristic of some distinct wines only. Especially, the question was addressed whether this vasodilatory effect might be a characteristic of those wines that are commonly consumed in countries where wine has been shown to lower the mortality of myocardial infarction. Furthermore, the study addressed the questions of whether vasodilatory effects of certain wines are dependent on endothelial function and whether they may be of relevance in humans.

Interestingly, vasodilatory effects were observed especially in those red wines that were produced en barrique, which means that the bunches of grapes are pressed and fermented with grape stems and that the wine matures in new oak barrels (2). This way of wine preparation is typical for Bordeaux, other areas in southern France, and some Italian wine regions. The procedure leads to a high concentration of phenolic...
components such as quercetin and tannic acid within the red wines (2). For the production of the Ahr-Spätburgunder, which had no effect on vascular tension in vitro, the grapes are typically pressed and fermented without grape stems, and the wine matures in steel tanks (2). Concerning its production, the Beaujolais Primeur is somehow between the "barrique" wine and the German red wine. The wine matures in steel tanks, but grapes are fermented together with the stems (2). Consequently, there was a significant vasodilatory effect of Beaujolais Primeur, but this effect was less pronounced than the effect of the red wines produced en barrique. From these observations, one might conclude that there are special substances within the grapes, but especially within the grape stems and the oak barrels, that are responsible for the vasodilatory effects of the particular wine. On the other hand, the Spanish white Rioja tested in this study is also produced en barrique but did not lead to a decrease in vascular tension. Obviously, some so far undefined mixture of substances typical for red wines is necessary to extract the vasoactive substances from the grape stems and the oak barrels.

This strict distinction between white and red wine is in some contrast to findings by Fitzpatrick et al. (10), who demonstrated that one of two white wines tested also had a vasodilatory effect. This effect was much less pronounced than the vasodilatory effects of red wines. However, this finding indicates that, possibly depending on the specific grapes used for wine preparation and depending on the handling of the grapes before fermentation, there might also be some minor content of vasodilatory substances in specific white wines.

The especially pronounced vasodilatory effect of the French and Italian red wines produced en barrique might explain why the effect of wine consumption on the mortality of myocardial infarction is more pronounced in France and Italy than in any other country (20, 28). It is interesting to speculate that it might not only be the higher amount of wine that is consumed in
these populations but also the preferred choice of wine that accounts for these differences. In consequence, if conclusions are drawn from epidemiological studies on the effects of wine consumption, the important aspect of different effects of different wines has to be taken into account.

In accordance with the observation that only certain wines cause vasorelaxation, ethanol in similar concentrations as in these wines had no effect on vascular tension. This observation supports the hypothesis that at least some wines are distinct from other alcoholic beverages concerning their vascular effects. The independence of the vasodilatory effects of wine from its alcohol content is in accordance with recent findings that not only wine but also grape skin extracts (even from white grapes) and several fruit and vegetable extracts induce vasodilatation in vitro (11). In consequence, it does not seem to be the fermentation process that is necessary to obtain beverages with vasodilatory properties but the content of vasoactive substances in their original ingredients and the specific preparation of these ingredients.

The results of this study suggest that the observed vasodilatory effect of barrique wines is mediated by endothelial generation and release of NO. It is known that NO is one of the most potent vasodilators, its effects being mediated by activation of the soluble guanylyl cyclase and enhanced production of cGMP, which in consequence leads to smooth muscle cell relaxation (6, 16). Evidence for the importance of endothelial function for the vasodilatory effects of red wine comes from the following observations: 1) the vasodilatory effects of the red barrique wines were dependent on the integrity of the endothelium; 2) the vasodilatory effects could be abolished by addition of the NO synthase inhibitor L-NMMA to the organ bath; 3) exposure of isolated vascular rings to red wine led to an increase in the vascular cGMP content; and 4) this increase in cGMP content was endothelium dependent and could be abolished by addition of L-NMMA to the incubation medium. Thus it appears that barrique wines cause a vasorelaxation because they are powerful modulators of endothelial function.

The question remains which pharmacological substances might be responsible for the vasodilatory property of red wine produced en barrique. The observation that two substances, tannic acid and to a minor degree quercetin, exert similar effects on rat aorta and human coronary artery vascular tension might suggest that those are representative for the vasodilatory substances in red wine.

Similar to the effects of barrique-produced red wine, tannic acid caused an endothelium-dependent vasodilation in rat aortic and human coronary artery rings, which was accompanied by an increase in vascular cGMP content and which could be abolished by L-NMMA. Thus effects of tannic acid on human and rat arteries seem to be identical to the effects of those wines that are known to have an especially high content of tannins.

In contrast, the vasodilatory effect of quercetin seems to be more complex and differs from the vasodilatory effect of red wine. Exposure to quercetin also leads to an increase in vascular cGMP content, which can be attenuated by inhibition of the NO synthase. However, this does not seem to be the relevant mechanism explaining its vasodilatory effect because this vasodilatory effect was independent from the integrity of the endothelium and could not be reversed by L-NMMA. These findings are in some points contradictory to those of Fitzpatrick et al. (10), who observed that mechanical endothelial denudation abolished the vasodilatory response of isolated rat aortic rings to quercetin. However, also in their hands, the effect of quercetin on rat aortic tension was not sensitive to NO synthase inhibition. One possible explanation for these differences might be an insufficient endothelial denudation by Triton X-100 treatment in the present series of experiments. However, the abolished vasodilatory response of vessel preparations to carbachol or substance P after Triton X-100 treatment indicates that there was no intact endothelium left. Thus an alternative mechanism has to be postulated by which quercetin leads to a decrease in vascular tone independent from endothelial NO generation. Because the phenol quercetin is lipophilic, it might directly interact with the sarcolemma of sarclemmal ion channels. Indeed, a variety of cellular effects have been demonstrated for plant phenols, including activation of sarcoplasmic reticulum Ca2+-ATPase (5, 35), inhibition of the Na+–K+–ATPase (27), and inhibition of phosphodiesterase (1).

The interesting observations in vitro led to the question of whether the observed effects could be of relevance in vivo. It has repeatedly been a matter of debate whether tannins or phenolic substances are absorbed from the intestine. Singleton et al. (32) observed an increase in serum tannic acid levels after addition of tannic acid to animal food. [4–14C]quercetin has been demonstrated to be absorbed in the intestine by 20% (37). Thus one might assume that substances contained in red wine undergo gastrointestinal absorption. In accordance with this theoretical consideration, there are observations in vivo that the consumption of grape juice leads to an inhibition of platelet aggregation in humans and dogs in vivo (12, 13). This effect, too, has been considered to be because of the high content of quercetin, catechins, and anthocyanins in grape juice. However, there is so far no direct proof that phenolic substances and tannins present in red barrique wine or other grape-derived beverages undergo gastrointestinal absorption. Also, it has to be pointed out that quercetin and tannic acid, which as purchased is a mixture of different tannins, have not been isolated from the different wines and therefore may differ from the phenols and tannins actually present in specific Barolo, Châteauneuf du Pape, or Bordeaux. Thus further studies will be needed in which the pharmacological substances present in red wine are characterized more precisely and in which absorption of these substances is demonstrated.
Despite the fact that substances that increase coronary blood flow may be beneficial for patients with coronary heart disease, one has to be very critical as to whether these vasodilatory substances also decrease the mortality of the disease. If the main mechanism by which red wine leads to vasodilatation is the generation of NO and activation of the soluble guanylyl cyclase, its effects can be compared with those of organic NO donors. These are used as standard substances in the therapy of coronary artery disease and lead to improvement of symptoms and physical capacity. However, so far there is no evidence that treatment of coronary heart disease with NO donors decreases mortality in patients (18). Thus the observed vasodilatory effects of some red wines seem to occur in concert with other mechanisms that may influence the progression of atherosclerosis by other mechanisms, e.g., blood lipid distribution and platelet function.

The use of vasodilators in the treatment of chronic heart failure might also be one limitation to this study. Because the human hearts were obtained from patients who had all been treated with angiotensin-converting enzyme inhibitors and partially been treated with nitrates, the endothelial response to the wines tested may differ from the response of vessel preparations not exposed to these pharmacological substances. However, in the absence of these drugs, which means in more contractile vessels, vasodilatory effects of red wine, tannic acid, and quercetin should be rather more than less pronounced.

In summary, this study demonstrates that red wine that is produced en barrique exerts a vasodilatory effect within a concentration range that could be reached in vivo by moderate wine consumption. Thus the consumption of some but not all wines may improve coronary blood flow and improve symptoms in patients with coronary heart disease. Because entirely different pharmacological effects are induced by different wines, the epidemiological data on the protective effects of wine consumption on cardiovascular events should be re-evaluated by taking into account the type of wine that is consumed. The isolation and further characterization of vasoactive substances occurring in certain red wines might help to characterize substances that are of benefit in the prophylaxis and therapy of coronary artery disease. Separation of these substances from the ethanol within red wine might allow the increase of the beneficial effects of these natural substances independent of the hazards of regular alcohol intake.

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